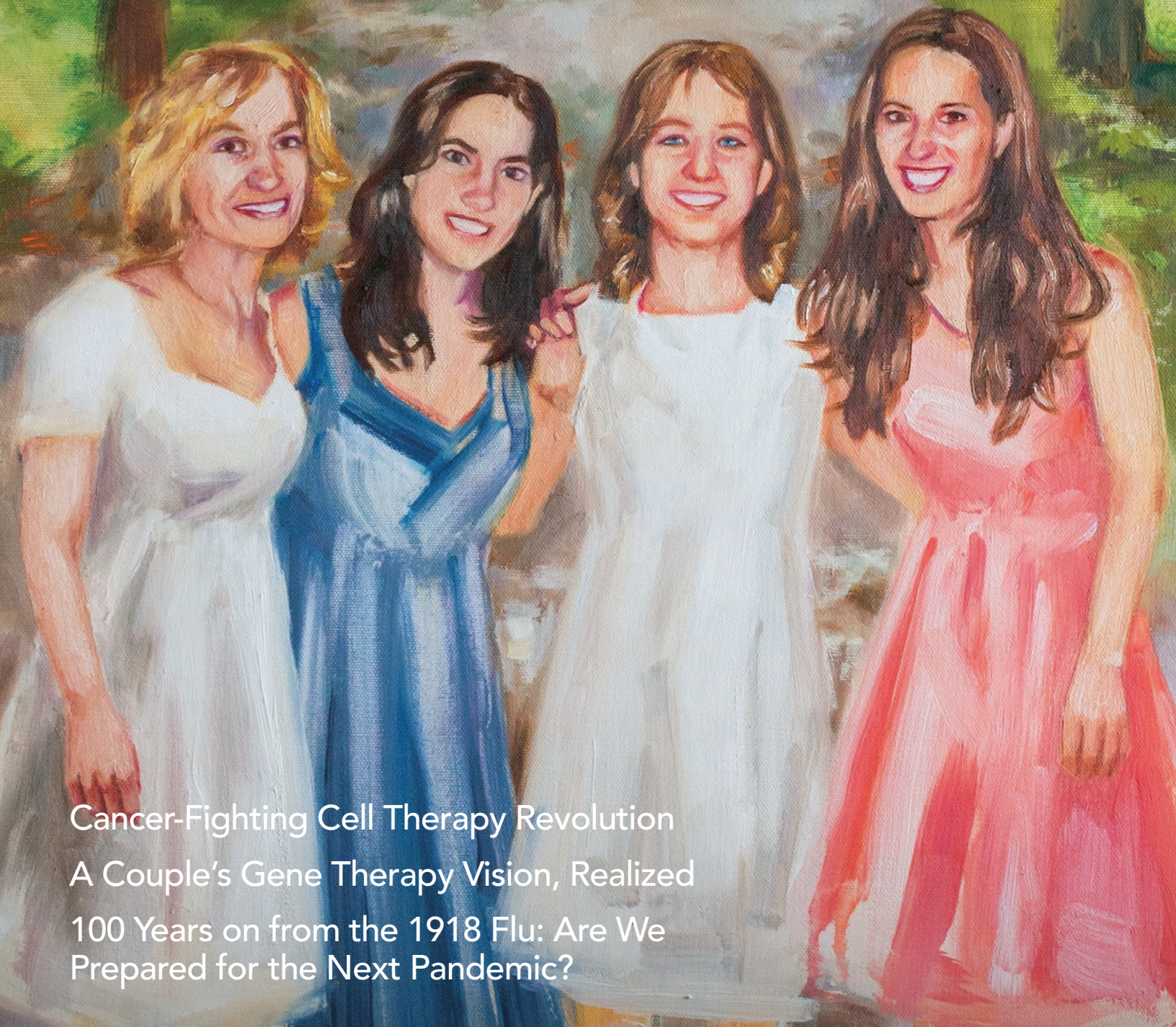


PENN Medicine



A FAMILY'S FATE

NEW HORIZONS FOR HEREDITARY CANCER



Cancer-Fighting Cell Therapy Revolution
A Couple's Gene Therapy Vision, Realized
100 Years on from the 1918 Flu: Are We
Prepared for the Next Pandemic?



Care in the Combat Zone By MaryKate Wust

“We were asleep in our tents and awakened by the humming of German motors. Then the bombs began to drop. We reached for our ‘tin hats’ that we always kept hanging on our cots along with our gas masks. Even with my eyes closed, I saw the flashes from the explosion. The concussion was terrific.”

The weary but steadfast hero hunkering down in a brief moment of quiet to commit to paper their story is a familiar trope in retellings of the so-called Great War. In this case, though, the author of the 1917 wartime diary entry was not clad in olive drab, but in a starched white apron. A 1912 graduate of Pennsylvania Hospital’s School of Nursing, Helen Grace McClelland volunteered alongside colleagues from her alma mater in response to the American Red Cross’s call for nurses to go abroad in 1914.

At this point, the U.S. considered the conflict a European affair and sought to remain uninvolved. McClelland was one of thousands of American women—professionally trained nurses and otherwise—who felt drawn to support the Allied cause as humanitarian aid workers. But no quantity of enthusiastic volunteers could make up for unsanitary conditions, a dearth of supplies, cramped quarters, and gruesome injuries and infections.

After a brief return home, McClelland again ventured overseas in 1917 as a member of the Army Nurse Corps. She was deployed near the Belgian front. Between catastrophic gunshot and shell wounds, severe gangrene, devastating chemical burns stemming from the widespread use of mustard and chlorine gases, and rampant viral and bacterial infections, time was of the essence to preserve life and limb. It was clear that more lives could be saved if wounded soldiers were treated at clearing stations on the front lines, rather than transported to faraway base hospitals—but that meant the medical personnel, too, were under the threat of attack:

That August, bombs struck less than 30 feet away from McClelland’s tent, the incident recorded in her diary. She

further recounted that when two bombs hit the cookhouse, shrapnel entered her tent and pierced the eye and cheek of Miss Beatrice Mary McDonald. Then, though made no note of it, rather than seeking shelter for herself, McClelland sprang to action, stopping the hemorrhaging of her tent-mate’s wounds and ultimately saving her life. She also rendered further aid to others, despite continued enemy fire as the base sustained heavy casualties.

Her heroism was later recognized with a Distinguished Service Cross—the country’s second-highest combat award—as well as a commendation from General Sir Douglas Haig and the British Royal Red Cross, First Class. She became one of the most decorated women of the war.

The wartime contributions of nurses like McClelland have been largely unrecognized or undermined by romanticized propaganda featuring angelic, rosy-cheeked young women. A new exhibition on display at Pennsylvania Hospital throws such experiences into sharp relief. The collection of photographs, correspondence, artifacts, and mementos focuses on the complex and challenging lives of the nurses grappling with nightmarish trench warfare injuries in France, as well as of those who remained on the home front to face supply shortages and a worldwide influenza pan-

demie that ultimately proved deadlier than the war itself. (See more about the influenza outbreak on p.32.)

“When you take in these stories of the part Pennsylvania Hospital’s staff played at home and abroad during this time,” said Stacey C. Peeples, curator and lead archivist of the hospital’s historic collections, “you really get the sense that no matter the crisis, we have historically pulled through and continue to do so.” □



The exhibition, “Pennsylvania Hospital and the Great War: Home and Abroad,” will be on display through December 2019 in the hospital’s Historical Library and Portrait Gallery in the Pine Building. Visit at 800 Spruce Street in Philadelphia. To learn more, contact Stacey Peeples at stacey.peeples@uphs.upenn.edu or 215-829-5434.



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A century ago, Penn medical students raced to treat an outbreak with few resources. Today, researchers are finding new ways to battle an old illness—because the threat of another major global pandemic is not as far in the past as we might think.

About the Cover: Love, loss, and connection among family members who have or are at risk for hereditary cancers are central motifs in our cover story about the Basser Center for BRCA at Penn's Abramson Cancer Center. This portrait of the Basser women, including the late Faith Basser, the center's namesake, was painted for *Penn Medicine* by Lizz Card. Card is a second-year medical student at the Perelman School of Medicine who was featured in the Spring/Summer 2017 issue of *Penn Medicine* for her artistic pursuits.

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Family Matters

Without even thinking about it, we're accustomed to thinking of the individual person as the social unit of medicine. Each patient has his or her own medical record, an individual history, a diagnosis (or a set of them), a treatment plan. One patient's name is written on the prescription. Likewise, each individual doctor earns a medical degree with her own name on it, an individual medical license, and perhaps leads an individual research agenda as a principal investigator.

We're used to things working this way, but it isn't the only way. The stories in this issue of *Penn Medicine* invite you to widen your perspective to take on the family around each individual.

Family is central to the experience of inherited diseases and inherited disease risk. As shown through a patient-family's moving example in our cover story about Penn's Basser Center for BRCA, mutations in the *BRCA1* and *BRCA2* genes, once discovered, ripple with implications among siblings, children, nieces and nephews, and generations to come. Entire families journey together through the experiences of genetic testing, decisions about preventive care, treatment when needed, and working with researchers toward ever-better options for future generations.

The cover art that accompanies the story, a portrait painted by Penn medical student Lizz Card, is another nod to the central importance of families in this issue. Portraiture has historically been a way that families could remember a loved one no longer with them; this one captures a happy moment with Basser family matriarch Pearl, who died last year; Faith, who the family lost to ovarian cancer in 2002; and surviving younger sisters Shari Potter and Mindy Gray. Mindy, with husband Jon Gray, established the center at Penn named in Faith's honor to advance research and care for BRCA-related cancer.

Family is inspiration—not just on the scale of grand investments like the establishment of the Basser Center, but on the most intimate level. Katie Magoon, a third-year medical student at Penn, grew up hearing her mother's stories about working as a physician when she had few women among her peers. As her mom's verbal communication ability began to decline due to Parkinson's disease, Katie was inspired to capture these stories and many more in an oral history project on women in medicine. (See more on p. 10 and listen to audio online.)



And family is sometimes the framework for how medical advances get made, as in the story of Jean Bennett, MD, PhD, and Albert Maguire, MD (p. 28). A couple who met and married during medical school, Bennett and Maguire joined forces to unite her skill in molecular biology with his as a retinal surgeon and work toward a shared vision—now achieved—of a gene therapy to reverse congenital blindness. Along the way, they leaned on one another's personal strengths, raised three children, and adopted two canine study participants into their family.

Perhaps most importantly, family can be the best of what great medical breakthroughs can offer. Just look at Bill Ludwig (p. 25), the first patient to participate in human trials of a now newly FDA approved CAR T cell therapy, in 2010. He was near death from leukemia at that time and out of options. But today he has had years more to spend with his wife traveling across the country. He has seen the birth of grandchildren he might have never met, and he has watched them grow. It would be true to say that a remarkable advance in medicine saved Ludwig's life as an individual—but family is what medicine gave back to him. ▽

RE

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Penn Ranked No. 4 Most Innovative University Worldwide

In an annual analysis by Reuters of the top 100 most innovative universities on the planet, the University of Pennsylvania placed fourth in 2017, up from eighth place in 2016. The ranking, compiled in partnership with Clarivate Analytics, is based on proprietary data and analysis of indicators including patent filings and research paper citations.



Penn Joins Coalition on Life Sciences Career Prospects

The University of Pennsylvania is one of 10 institutions that announced plans to give would-be life scientists clear, standardized data on graduate school admissions, education and training opportunities, and career prospects. The group, including Cornell, Duke, the Fred Hutchinson Cancer Center, Johns Hopkins, UCSE, and several others, is forming the Coalition for Next Generation Life Science in response to the lack of good marketplace information on training and career options for talented life scientists; many new PhDs focus solely on a limited number of traditional faculty positions. Penn President Amy Gutmann was one of the authors of the article announcing the coalition, in *Science* in December 2017.

The coalition members will issue statistical reports in an open, standardized format, with information on admission and enrollment, demographics of graduate students, time spent in postdoctoral fellowships, and jobs held by an institution's former graduate students and postdoctoral fellows. Each coalition member has also agreed to help graduate students and fellows better explore alternative career paths such as careers in industry, entrepreneurship, and government; improve mentoring; and work to improve diversity in the life sciences workforce. Because similar academic workforce challenges are applicable to disciplines outside of biomedical science, the coalition's work could extend in the future to graduate education and training in the natural and physical sciences, engineering, the social sciences and the humanities.



It's Official: Penn Medicine Princeton Health

Princeton HealthCare System (PHCS) and its affiliates are now part of the University of Pennsylvania Health System, leaders from both health systems announced on Jan. 9, 2018, after receiving all necessary regulatory approvals. As part of this transaction, the names of PHCS and its affiliates have changed. The system is now Penn Medicine Princeton Health, while its hospital, University Medical Center of Princeton, is Penn Medicine Princeton Medical Center. UPHS CEO Ralph W. Muller described the joining as "an exciting new chapter in Penn Medicine's growth." It broadens Penn Medicine's reach across the Philadelphia region from Lancaster General Health in south central Pennsylvania, approximately 80 miles west of Philadelphia, to the Princeton system in central New Jersey, approximately 50 miles northeast of Philadelphia.

Suzanne Rose Named Senior Vice Dean for Medical Education



Suzanne Rose, MD, MSEd, a renowned leader in medical education, has been named senior vice dean for Medical Education at the Perelman School of Medicine.

Rose begins at Penn in February 2018. She most recently served as senior associate dean for Education at the University of Connecticut School

of Medicine, where she was nationally recognized for spearheading a highly successful curriculum reform effort. She previously held leadership positions at Mount Sinai and the University of Pittsburgh. Rose is a graduate of the University of Pennsylvania, with a Bachelor of Arts in Russian Language and Literature and a Master of Science in Education. She received her medical degree from Case Western Reserve University followed by residency in internal medicine and a postdoctoral fellowship in gastroenterology. Her scholarship has a sharp focus on medical education, crossing the intersecting domains of women's issues in health, undergraduate and graduate medical education, evaluation of educators, and developing the next generation of health care leaders.

"We are thrilled to welcome one of the nation's most talented leaders in medical education to Penn Medicine. Dr. Rose is nationally recognized as an

inspirational and collaborative leader with a strong track record of fostering transformative change," said J. Larry Jameson, MD, PhD, dean of the Perelman School of Medicine and executive vice president of the University of Pennsylvania for the Health System.

Rose will succeed Gail Morrison, MD'71, who remains at the Perelman School of Medicine and is taking on a new leadership role in online education. In thanking Morrison for her more than two decades of leadership and service to the school in medical education, Jameson said, "I am confident that she will once again pioneer important new methods of learning that will have a major impact at Penn and beyond." A celebration of Morrison's accomplishments and impact in medical education will be held in the spring. More information about her new online education program will appear in the Spring/Summer 2018 issue of *Penn Medicine*.

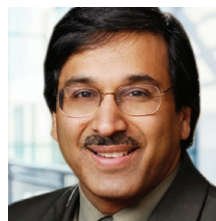
Rustgi and Li Named Fellows of the American Association for the Advancement of Science

Four University of Pennsylvania faculty members have been named Fellows of the American Association for the Advancement of Science. Election as an AAAS Fellow is an honor bestowed upon members of AAAS, the world's largest general scientific society, by their peers. Two of this year's fellows are from Penn Medicine.

Anil K. Rustgi, MD, the chief of Gastroenterology and T. Grier Miller Professor of Medicine and Genetics, was selected for accomplishments in cancer biology, including the identification of a protein located in the cytoplasm of cells, p120 catenin, as a tumor suppressor, and for insights into the tumor microenvironment.

Hongzhe Li, PhD, a professor of Biostatistics, was selected for distinguished contributions to methods in statistical genetics, modeling of high dimensional genomic and metagenomic data, and promotion of statistical reasoning in society.

Fellows will be formally recognized on February 17 during the 2018 AAAS annual meeting in Austin, Texas. New AAAS fellows from other Penn schools are Gustavo D. Aguirre, VMD, PhD (Veterinary Medicine) and Daniel José Mindiola, PhD (Arts and Sciences).



Anil K. Rustgi



Hongzhe Li

The Pavilion



Construction Update

The first steel girders are in place for the Pavilion, Penn Medicine's \$1.5 billion inpatient tower opening in 2021.

But that is just the tip of the iceberg!

Project will use approximately
16,000 TONS
of steel

67,000
erectable pieces of steel

Single heaviest piece delivered:
68.7 TONS

Five PSOM Faculty Members Elected to National Academy of Medicine

Seven University of Pennsylvania faculty members have been elected to the National Academy of Medicine (NAM), one of the nation's highest honors in biomedicine. They are among 70 new U.S. and 10 international members of the globally renowned organization. Five of these seven new members are from the Perelman School of Medicine, bringing Penn Medicine's NAM membership to 66 of the total 2,127 members worldwide.

Lewis A. Chodosh, MD, PhD: His research focuses on mechanisms of cancer progression using basic, translational, and clinical approaches, with an emphasis on preventing and treating breast cancer recurrence. Chodosh is the chair of Cancer Biology, associate director for Basic Science in the

Abramson Cancer Center, and co-director of the 2-PREVENT Translational Center of Excellence.

Christos Coutifaris, MD'82, PhD'84: His research focuses on understanding the cellular and molecular basis of human trophoblast function (nourishment supply for the embryo) and abnormal development of the placenta. Coutifaris is the Celso Ramon Garcia Professor of Obstetrics and Gynecology and chief of Reproductive Endocrinology and Infertility.

Maria A. Oquendo, MD, PhD: Her research is on the neurobiology and pharmacologic treatment of mood disorders, with an emphasis on suicidal behavior and global mental health. Oquendo is the Ruth Metzler Professor and chair of Psychiatry.

Michael S. Parmacek, MD: He has made key discoveries for understanding the molecular and genetic basis of congenital heart disease, atherosclerosis, aortic aneurysm and dissection, and heart failure. Parmacek is the Frank Wister Thomas Professor of Medicine and chair of Medicine.

Flaura K. Winston, MD'90, PhD'89: Her research includes improving child-passenger safety, preventing teen and young-driver crashes, and addressing post-traumatic stress after injury. Winston is a professor of Pediatrics at the Perelman School of Medicine and the founder and scientific director of the Center for Injury Research and Prevention at Children's Hospital of Philadelphia.

New NAM members from other schools at Penn this year are Therese S. Richmond, PhD, CRNP, FAAN (Nursing) and Dorothy E. Roberts, JD (Law, Arts and Sciences).



Lewis A. Chodosh



Christos Coutifaris



Maria A. Oquendo



Michael S. Parmacek



Flaura K. Winston



In a moment that went globally viral, former Vice President Joe Biden moved to sit beside Meghan McCain and held her hand as he consoled her over her father's battle with glioblastoma during an appearance on "The View." Biden pointed to CAR T cell therapy and other ongoing work at the Abramson Cancer Center as reasons for hope in the fight against cancer. Biden leads the Penn Biden Center for Diplomacy and Global Engagement.

The touching moment connecting the family cancer journeys of the Bidens and McCains showed that "cancer doesn't side with any one political party," Robert Vonderheide, MD, DPhil, director of the Abramson Cancer Center, wrote in the *Philadelphia Inquirer* soon thereafter. "It has no bias, no ability to discriminate." Emphasizing that sustained philanthropic and government support is essential to drive the breakthroughs that offer patients hope, Vonderheide called on Congress to reach across the aisle to support medical research funding, inspired by this example of bipartisan humanity and hope.

Oncology Chief Lynn Schuchter Receives FOCUS Award for Advancement of Women in Medicine

For Lynn Schuchter, MD, whose career has been dotted with high accolades for her achievements as an oncologist and clinical researcher, the 2017 FOCUS Award for the Advancement of Women in Medicine is one of the most meaningful awards of them all.

FOCUS, a group at the Perelman School of Medicine centered on the advancement and leadership of women in academic medicine, and on research and education in women's health, confers the award annually to a faculty member whose outstanding efforts and achievements have promoted the career success, leadership, and overall quality of life for Penn women in academic medicine.

But in accepting the award, Schuchter turned the tables and credited FOCUS for empowering her to reach for her own leadership potential.

"Without FOCUS, I would never have become the chief of Hematology/Oncology," said Schuchter, who in addition to being division chief is the C. Willard Robinson Professor of Hematology/Oncology. The group introduced her to role models who were women in leadership roles, and it gave her the courage to consider applying for the position and the confidence to know she could build a strong team to handle the job's novel challenges. She now leads more than 100 faculty who see more than 90,000 patients per year, and she oversees a \$25 million research budget, while leading her own robust research in melanoma.



At the Philly Fights Cancer gala in October 2017, Schuchter was honored as an inspiration to cancer fighters across the region.

Schuchter was selected for the FOCUS award due to her commitment to and passion for mentorship and for her record of training physicians and scientists interested in both translational and clinical oncology research. Her guidance has helped her mentees obtain international recognition as well as leadership positions of their own. She has also worked to create networking opportunities for women through informal gatherings in her home and through career development sessions for women at the national Society for Melanoma Research. One of her nomination letters summarized her as a "beacon for professional women," and the FOCUS leadership team added in announcing the award, that she is also "a beacon for all faculty at the Perelman School of Medicine."

Yet in a fitting coda to some of the very reasons she has served as a role

model to so many women at Penn Medicine, she did not attend the FOCUS fall conference event where the award was presented to her; she had a prior commitment to tour colleges with one of her 18-year-old twin sons. She sent her regrets—and her appreciation for the award—in a video message. In that message, Schuchter said she knew that her peers would understand that spending time with family was the right choice to make in this case, and that such choices of balance are an everyday aspect of the professional medical life. At another event this fall where Schuchter was an honoree, the Philly Fights Cancer fundraiser for the Abramson Cancer Center, her sons were in attendance. "I think they feel proud of the work that I'm doing," she said. "I've shared with them that I hope they find a career as satisfying and nourishing as mine has been for me."

What lies ahead for medicine at Penn in 2018?

Schuchter's take: "While I am so excited about the new developments in treatment for patients with melanoma, I am most excited about the work we are doing in implementing the Serious Illness Conversation Guide for all of our Hematology Oncology practitioners. This is a framework for clinicians to explain serious illness, like cancer, to patients so that they have a good understanding of their illness. It also ensures that the clinicians know the goals, values, and priorities of their patients. The goal is to have more, better, and earlier conversations about illness. This is hard work but so important."

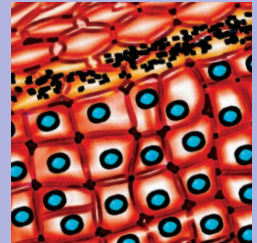
► Find more Penn Medicine predictions for 2018 on the Penn Medicine News Blog. For the link, visit PennMedicine.org/magazine/winter18vs.

Research Countdown

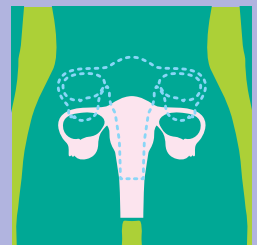
\$2,000 or higher out-of-pocket costs for oral cancer medications were associated with nearly half of patients failing to pick up their prescription, according to a Penn study published in the *Journal of Clinical Oncology*. Ten percent of patients abandoned prescriptions even when costs were under \$10. The researchers emphasize the need for clinicians to discuss financial barriers when planning treatments and for multiple stakeholders to address barriers to patient access.



42 distinct tissue types from over 400 healthy donors are represented in new data generated and studied by the Genotype Tissue Expression (GTEx) consortium, in which Penn is one of four core collaborating institutions. GTEx published a comprehensive atlas of variation in gene expression in *Nature* and *Nature Genetics*. The Penn group is focused on finding associations between genetic variation and gene expression in healthy tissue in order to identify mechanisms behind variations involved in disease.



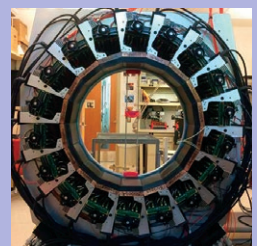
35 providers or more will be involved in the care of each patient in Penn Medicine's new uterine transplant trial. The trial provides a new path to parenthood for women with Uterine Factor Infertility, an irreversible form of female infertility. Participants will work with the multidisciplinary team of specialists for years, from eligibility screening through potentially the Caesarian delivery of up to two children, followed by hysterectomy to remove the transplanted uterus.



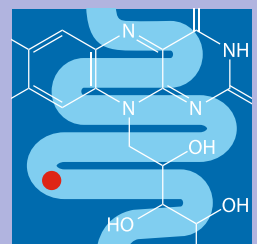
3 projects using behavioral economics in mental health service delivery—focused on improving antidepressant medication adherence and the use of evidence-based services for school-aged children with autism and among mental health practitioners—launch the new Penn ALACRITY Center. It is one of two funded by the National Institute of Mental Health.



2 of the key food sources consumed by cancer cells, glucose and glutamine, can be analyzed for their simultaneous metabolism thanks to a new Moonshot grant for imaging research at the Perelman School of Medicine. Researchers at Penn are building a positron emission tomography scanner that can image a patient's entire body at once, including glucose and glutamine, which currently can only be measured in separate scans.



1 single bacterial enzyme called urease could be key to imbalance in the gut microbiome linked to Crohn's disease. A new Penn-led study published in *Science Translational Medicine* suggests that wiping out a significant portion of the bacteria in the gut microbiome, and then re-introducing a certain type of "good" bacteria that lacks urease, may be an effective approach to better treat these diseases.



Honors & Awards



Deborah A. Driscoll, MD

Luigi Mastroianni Jr. Professor and Chair, Obstetrics and Gynecology

2017 Leadership Award for an Individual

The Group on Women in Medicine and Science, a professional development group of the Association of American Medical Colleges, honored Driscoll for impact on the advancement of women's roles in academic medicine and science.



M. Celeste Simon, PhD

Arthur H. Rubenstein, MBBCh Professor, Cell and Developmental Biology; Scientific Director, Abramson Family Cancer Research Institute

National Cancer Institute Outstanding Investigator Award

The award funds Simon's basic biomedical research on cancer metabolism, specifically renal cancer, which is one of the ten most common cancers in both men and women.



Jonathan A. Epstein, MD

William Wikoff Smith Professor of Cardiovascular Research; Executive Vice Dean and Chief Scientific Officer

NHLBI Outstanding Investigator Award

In granting this highly competitive award, the National Heart, Lung, and Blood Institute (NHLBI) described Epstein as "a gold standard role model for physician-scientists in the field."



Louis J. Soslowsky, PhD

Fairhill Professor of Orthopaedic Surgery; Associate Dean, Research Integration

H.R. Lissner Medal

The American Society of Mechanical Engineers confers the medal to recognize outstanding achievements in the field of bioengineering; it is widely viewed as the highest honor in the bioengineering community.



Chantell Evans, PhD

Postdoctoral Fellow, Physiology (Erika Holzbaaur Lab)

Hanna Gray Fellow

The Howard Hughes Medical Institute (HHMI) named Evans as one of 15 early-career scientists in its first cohort the fellowship that includes up to \$1.4 million in funding over eight years, with mentoring and active involvement within the HHMI community.

LETTERS

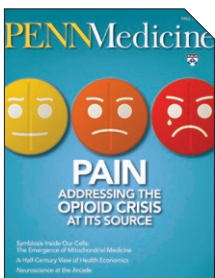
Learning from "Special" Diseases in History

Excerpts from a response to "Cancer and the Costs of Special Treatment" by Janet Weiner, PhD (Penn Medicine, Fall 2017). Read the letter in full online.

"At various times in history certain illnesses have provoked more fear than others and so earn the title 'special...'. Tuberculosis perhaps most closely resembles the current attitude toward cancer." It acquired an aura of fear as well as romantic connotations, influencing art and literature. "More importantly, from a medical perspective, the 'specialness' of the disease spurred research and laid the groundwork for much of modern microbiology (e.g., Koch's bacillus), leading to vaccination and antibiotics."

"The 'fallout' from the allocation of resources to research 'special' diseases is not always predictable and may have influence far beyond the treatment for the 'feared' disease (as Dr. Weiner points out in her article). Finding the proper balance between costs and benefits is not easy. Adding an unknown factor (the accrual of basic science and medical knowledge) further confounds the problem. The Gant consortium is to be commended for taking on this difficult, multifaceted conundrum."

Edward W. Gerner, MD, GME'69





Industry and Government's Role in Crisis; Strategies for Bioenergetic Medicine

Excerpts from responses to "Prevention at the Point of Pain" by Mark Wolverton and "Our Electric Symbionts and their Rebel Champion" by David Steen Martin (*Penn Medicine*, Fall 2017). Read the letters in full online.

On opioids:

After watching investigative reports based on information from a DEA whistleblower by "60 Minutes" on CBS in collaboration with the *Washington Post*, "my opinions about the role of the physician as the primary change agent who can address the opioid crisis radically changed....A massively larger source of the crisis was the promulgation of intentional, malevolent, and greed-induced policies fostered by the United States government."

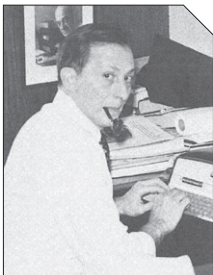
The *Penn Medicine* article "suggests that physical therapy, cognitive based therapy, social programs, and multifaceted addiction treatment simply need to be better coordinated. This exercise in futility is analogous to simply mopping up faster in the face of seeming total inability to turn off the fire hose soaking the country in opioid addiction."

On mitochondrial medicine:

"Many effective therapeutic strategies have been identified. A diet high in plant-based proteins, fats, and complex carbohydrates is essential, for antioxidants and natural anti-inflammatories."

The article implicates "naysayers" who question Douglas Wallace's emphasis on mitochondria in disease. "I wonder if these naysayers have any allegiance to maintaining the status quo conventional disease-care model. I look forward to research outcomes which might elucidate etiologic factors and provide clinical recommendations for targeted practical and lower-cost behavioral changes that could slow/reverse mitochondriopathies, rather than predictably simply seek a billion-dollar pharmaceutical 'solution.' This burgeoning field deserves more than just a magic pill."

L. Matthew Schwartz, MD, GME'89



Albert Winegrad's Legacy of Mentorship

We were saddened to learn of the death of Albert I. Winegrad, MD, formerly Willard and Rhoda Ware Professor of Diabetes & Metabolic Diseases, and director of the George S. Cox Medical Research Institute. His obituary published in the last volume of *Penn Medicine* failed to note one of Dr. Winegrad's important but unsung contributions to the School of Medicine, his mentoring of future physician-scientists at all levels, medical students, residents, fellows and junior faculty.

Each of us was touched by Dr. Winegrad while we were medical students at Penn, and each of us is profoundly grateful for the influence he had on our career choices. Despite his international reputation in diabetes research, particularly the pathophysiology of diabetic neuropathy, Winegrad was not visible to medical students. He was not outgoing to say the least; you had to be directed to him by one of the cognoscenti.

Those who were fortunate to find their way to his laboratory were richly rewarded. His office door opened to his laboratory so he could observe all that was going on, which he did. Although the door was always open, if you wanted to speak with him you had to navigate a maze made up of stacks of [journals] to get to a chair. The maze, no doubt, was the physical embodiment of his personality—not easily approached, guarded and shy. However, once the maze was traversed and the seat taken, he would open up and dispense invaluable wisdom.

A meeting with Dr. Winegrad was filled with probing questions about experimental design or results; insightful critiques of recent publications; and, usually, his commentary, often stinging, on the state of medical education and research. But above all, these séances were about teaching critical thinking, and instilling a passion for translational research, well before that term became common parlance. You walked away from the meeting a little humbled, but exhilarated about the science.

Michael S. Brown, MD'66

Edward W. Holmes, MD'67

Jerome F. Strauss III, MD'73, PhD'75, GME'76

► Find the full-length versions of the above letters online, along with individual remembrances of Winegrad by Brown, Holmes, and Struass, at PennMedicine.org/magazine/letterswinter18.

Policy, People, Podcasts, and Practice

By Isabella Cuan

Photos by Peggy Peterson

Penn medical student Katie Magoon is combining a background in nursing and health policy with audio storytelling through an oral history project with women in medicine.

Katie Magoon, RN, NP, MPA, was raised in Canton, Ohio, in a family of physicians and health care professionals, a world in which family dinners in the hospital cafeteria were the norm. Such an early exposure to the health care system gave her a nuanced understanding of the field and fueled her desire to be a part of it. Yet Magoon's path in health care has been far from traditional. And though her diverse experiences and interests in health care have led her many places, from health policy to nursing care for vulnerable populations, they have ultimately converged in her latest adventure as a doctor-in-training at the Perelman School of Medicine.

Now, as a third year medical student, Magoon strives to contextualize all of her interests in the world of science and medical practice. Deeply passionate about working with people and storytelling, Magoon has spearheaded an oral history project, engaging with and recording stories about women in medicine.

How did you develop an interest in medicine?

In college, I thought that I was going to be doing health policy and be a kind of policy wonk for the rest of my life,

and then I was introduced to nursing and decided to attend Yale School of Nursing. I then moved to New York, where I worked as a nurse practitioner in adolescent family planning and adolescent HIV clinics, as well as in adolescent transgender care, at SUNY Downstate and Brooklyn Hospitals. Because of where I worked, I was able to pursue a degree in health policy. While obtaining my master's in health policy while working as a nurse practitioner, I fell in love with actually practicing medicine. I started to realize that if I want to treat someone for HIV, I wanted to be a lot more comfortable with a lot of the hard science behind the medications we use. A lot of nurses do have that background, but I didn't because of my policy background. So I decided to throw myself into science and went to medical school and came here for Penn Med, and somehow they let me in!

Did you ever envision yourself doing anything other than health care?

I always thought I'd be doing some kind of health policy or provision of care and I would like to continue to merge both. I love working with people, I love hearing their stories, and I also love thinking about more macro-level issues. For me, it makes more sense to think

about those issues if I also have my feet on the ground for a little while.

Tell me more about the oral history project you are spearheading and the inspiration behind it.

It was really inspired by my mom. She was in that class of '70s women going to medical school when it really was mostly men, and she has a lot of stories about that. And I grew up hear-



Martha Magoon, MD, and Katie Magoon.

ing those stories and thinking a lot about what it meant to be a woman in this medical world.

My mom was diagnosed with Parkinson's disease over 20 years ago, and she is getting to the point where it is difficult to communicate. My mom has always inspired me because she was an English major in college and has always been a phenomenal writer. As a doctor,

she has always used incredible communication abilities to improve the care that she provides for patients. And even when she wasn't able to physically do a lot of that anymore, she would do things like teaching and writing. And that [desire to capture her stories while she can still communicate] is really what inspired me to start this project. Also, in talking to my classmates in school, I learned that we actually have a lot of moms who were these first female physicians [in predominantly male cohorts]. So I thought that if I am this influenced by one person, then what would it be like to have oral histories of all these other women in medicine?

How did you initially get the project off the ground? Where are you with it now?

We started off with a small cohort of people at Penn Med who were interested in getting these stories down, and now we are trying to record stories from women all over the world. We aren't exactly sure what we want to do with them yet, but it's been really fun so far to get them recorded.

It has been really powerful because it is a great reminder, while on the day-to-day grind of being in medicine, that this is something that has affected these women, and has shaped their lives in a really beautiful and powerful way. I think we would be remiss if we didn't record it. It's an important part of history.

For example, my mom would always say that people expected her to drop

afraid to interact with these patients, and how that influenced how they viewed themselves as physicians. Since I also worked in the HIV world, I am particularly interested in this.



You are also a podcast producer for Doctors Who Create. What does your role entail and how do you see this relating to your other interests?

From the time I was little, the thing I would get in trouble for most was socializing and chatting too much. When one of the surgeons I worked with gave me feedback, he said you definitely have the "gift of gab." Not sure it was a com-

but everyone will tell you that you get the diagnosis from the history. As a doctor, it's so important to effectively communicate, so I've tried to take that seriously and challenge myself with

that. It all ties together because of the importance of communication and storytelling in medicine.

Do you have any pieces of wisdom to offer others pursuing this path?

Life is too short to not go for what you want. Especially as women, we sometimes—and I have even found myself—don't do that. And when I take a step back and reassess, I am always glad when I am thoughtful about what I want and who I am, and really going for it in an honest way. Life's too short to not go for your dreams. ☺

“It all ties together because of the importance of communication and storytelling in medicine.”

out of medical school once she got married. But she kept going, and luckily had the support of her feminist husband. Another interesting thing that sprung up was that a lot of these women practiced throughout the start of the HIV epidemic, so we are thinking about starting another project specifically about the HIV epidemic and what it was like to practice in the beginning of it when people were truly

pliment, but that's fine! I love getting to know people and hearing their stories and doing that while being recorded is a little awkward but a fun challenge. Terry Gross [host of "Fresh Air" on NPR] is one of my heroes. I admire the way that she asks poignant questions in a sensitive and non-judgmental manner, while also using humor and kindness to connect with her guests. As physicians, we have lab values, and physical exams,

Isabella Cuan is a pre-medical student at the University of Pennsylvania studying neuroscience and art history, and a staff writer for Doctors Who Create, a website founded by Penn medical student Vidya Viswanathan. This story was produced as part of a partnership between Penn Medicine and Doctors Who Create, and is jointly published online.

► **Find the extended version with extra photos and audio selections from Cuan and Magoon's conversation at PennMedicine.org/magazine/magoon.**

By Jill Neimark and Rachel Ewing

Painting by Lizz Card

FAITH, FATE, AND



The Basser women: Pearl Basser with her daughters Shari, Faith, and Mindy.

Faith Basser died in 2002, at age 44, of ovarian cancer. She left behind a young son and a devoted husband, her parents, and three siblings, including two younger sisters. Shari, seven years younger, and especially Mindy, 12 years younger, had grown up seeing Faith as much as a mother figure as a sister, best friend, and partner in adventure.

The family's loss came with one extra kick.

"We knew nothing of BRCA gene mutations when we lost Faith," says Mindy. "We only learned then that this mutation is hereditary and can lurk beneath the surface, silently passed down from generation to generation."

Through a series of fateful events, Faith's death ultimately led to the establishment, in 2012, of the Basser Center for

BRCA at the University of Pennsylvania's Abramson Cancer Center as the world's first center devoted to the study of BRCA-related cancers. In its first five years, led by Executive Director Susan M. Domchek, MD, the Basser Center has built on Penn's long prominence in BRCA research to spearhead standards for prevention, screening, and treatment for men and women with these gene mutations. Its unique bench-to-clinic model of cancer care supports entire families—mothers, daughters, and sisters in particular—through the challenges that an inherited high risk of cancer presents. Today, it is clear that the center's work has implications not just for cancers caused by BRCA mutations, but for the cancer world writ large.

FAMILIES

At the Basser Center for BRCA at Penn, a unique philanthropic investment is making rapid progress toward new horizons in preventing and treating heritable cancer.

Risk that Ripples through Families

“It’s harder to find out your sister has cancer and a BRCA mutation than to find out for yourself,” says Laura Temple, a Basser Center patient who is in a position to know. Temple discovered that a mutation in the *BRCA2* gene ran in her family during her own course of treatment for breast cancer. She found a lump in her breast just six months after losing her mom to ovarian cancer in 2009. The youngest of her three sisters, Jen Schmidt, tested positive for the mutation soon after Temple did. Schmidt discovered she had breast cancer, too, upon her first mammogram after her genetic test.

BRCA stands for BReast CAncer susceptibility gene. Both of the two BRCA genes, *BRCA1* and *BRCA2*, are tumor-suppressor genes. In their normal form they help prevent cancer from developing. But certain inherited mutations on the genes can disable an important DNA repair process and dramatically increase the risk of breast and ovarian cancer, as well as some other cancers. Women with a *BRCA1* mutation have a 60 to 80 percent lifetime risk of breast cancer and a 20 to 45 percent lifetime risk of ovarian cancer. Women with a *BRCA2* mutation like Temple and Schmidt have a 50 to 70 percent lifetime risk of breast cancer and a 10 to 20 percent lifetime risk of ovarian cancer. BRCA mutations can be passed down by either parent to sons and daughters. For males, the risk of BRCA-related breast cancer is higher than normal, but still low; however, aggressive prostate cancer risk is significantly elevated. Both men and women with BRCA mutations have a higher risk of pancreatic cancer and melanoma than the general population.

What we know about the BRCA gene mutations began with familial studies of breast and ovarian cancer and a flurry of competitive research to identify the underlying genes in the early 1990s. Penn has been at the forefront of such re-

search since the beginning; among the researchers who identified *BRCA2* as a breast cancer susceptibility gene was Barbara L. Weber, MD, a longtime Penn researcher who left for industry in 2005 and who was a mentor to both Domchek and Katherine L. Nathanson, MD’93, director of genetics at the Basser Center and deputy director of the Abramson Cancer Center.

Though BRCA genetic testing has been available for more than two decades since then, most people at risk for carrying a mutation have not been tested. A family history of breast or ovarian cancer is a ‘red flag’ that a BRCA mutation might be present. But not every family has an extensive, known health history. The Basser siblings—sisters Faith, Shari, and Mindy, and their older brother, Stephen—were the children of first-generation immigrant parents who, like many families, didn’t keep a written family history or know about early cancer deaths in past generations. The only known risk factor was that their ancestry was Ashkenazi Jewish, originally from Eastern Europe, one of a handful of groups known to have a higher frequency of BRCA mutations than the general population. Nobody knew that Faith had inherited one of these vulnerable genes until after she passed away. Likewise, even after Temple and Schmidt’s mother died of ovarian cancer, nobody in the family underwent genetic testing until Temple herself was in treatment for cancer.

Once a person discovers she carries a BRCA mutation, the discovery has rippling effects through families. Genetic counselors work with patients to guide conversations about testing for at-risk family members. These family members in turn may begin their own journeys through the choices

The center’s unique bench-to-clinic model of cancer care supports entire families—mothers, daughters, and sisters in particular—through the challenges that an inherited high risk of cancer presents.

of testing, screening, and, in some cases, cancer treatment or preventive surgical procedures. These conversations are infused with and informed by knowledge about risk and prevention in areas where Penn has led for decades, such as with models to predict the risk of carrying *BRCA1/2* mutations, and with research to understand the elevated cancer risks associated with *BRCA1/2* mutations, as well as in work pioneering the use of risk-reducing prophylactic surgeries based on empirical data. For families having these discussions about their evolving clinical options to deal with a BRCA mutation, the ripple effect can be daunting—the shadow of a deadly disease stalking them with the possibility of future losses. But it can also be a source of strength and connection.



Photo by Peggy Peterson

Susan Domchek, MD, executive director of the Basser Center for BRCA

Mindy and Jon

One great ripple from Faith Basser's death, as her family mourned her, was that it spurred her sisters, Mindy and Shari, into action that is evident in the existence and activities of the Basser Center. But the first stones that shaped that ripple dropped much earlier.

Pearl and Philip Basser raised their family in Center City Philadelphia, working hard and sacrificing so their children could have opportunities and education. Mindy, the youngest, adored and admired Faith. When Mindy was a child, she and Faith shared late-night binges on macaroni and cheese, watched soap operas, and often took long walks together. One season they walked so much, eyes to the ground, collecting candy wrappers around the city, that they reached their goal of 500 to win a prize.

In 1992, on another long walk, fate and Faith mingled in a vital moment in Mindy's relationship with a new beau. A senior English major at Penn, Mindy had been dating a classmate, Jon Gray, only three weeks when the young couple flew to Florida on \$99 travel vouchers to visit Faith. It was Mindy's idea to walk along the highway back to Faith's house after seeing a Steve Martin movie, *Father of the Bride*. "She's a big walker, and I was just learning that," says Jon, "and I

"We're in it for the long term with families. We're with these women through dating, marriage, and children. It's a true privilege that happens so rarely in medicine." – Susan Domchek, MD

turned to Mindy and said, 'I know we've only just met but I'm planning on spending the rest of my life with you.'"

The couple's relationship continued to deepen, strengthened by their similar values, including a central focus on family and on education. The couple moved to New York after graduating and married in 1995. By the time Faith died, the Grays were raising their first three daughters, Mindy worked in editing and marketing, and Jon was making a name in real estate for himself and his employer, the Blackstone Group.

After Faith died, the couple was spurred to action. They not only gave their fourth daughter the middle name Faith in her honor, but became supporters of research into her illness and the gene that put her at risk. Mindy began volunteering for the Ovarian Cancer Research Fund Alliance, eventually becoming a member of the executive board of directors. But in these efforts, over a span of years, she and Jon noticed that information about new research and resources for counseling families with BRCA mutations like Faith's were largely separate. There was no central hub for BRCA.

Then came another fateful day. One summer morning, Mindy was having tea and breakfast when Jon came in from a run. "He was so excited," Mindy says. "He said to me, 'I've had an epiphany. We are going to found the Basser Research Center—the BRC for BRCA.'"

They would fund a major center for counseling, research, cancer prevention and treatment for those with BRCA mutations, and name it after Faith.

"I welled up with tears," recalls Mindy.

Mindy and Jon's contributions to establish the Basser Center and commitments in support of its ongoing work since then now total \$55 million.

A New Kind of Family Medical Care

For Laura Temple, the discovery of her BRCA mutation during cancer treatment meant, first, pursuing a more aggressive course to prevent future cancers—a double mastectomy, when initially she'd hoped for a "band-aid" lumpectomy. The next ripple was seeing her youngest sister, Jen Schmidt, begin breast cancer treatment while she was still undergoing her own. As time went on, the shared BRCA experience also brought the sisters together.

Now seven-year survivors of their breast cancer treatments, Temple and Schmidt share the experience of seeing Susan Domchek at the Basser Center for their follow-up care. So does another sister, Sarah Matos, who was treated



Seeing Your #InvisibleGenes

On Nov. 14, 2017, Mindy and Jon Gray addressed a sold-out crowd of over 1,100 people at the second biennial Basser Jean Bash, a fundraiser for the Basser Center for BRCA. In addition to celebrating five years of remarkable progress in the understanding, prevention, and treatment of BRCA-related cancers since the couple established the center in 2012, the Bash featured the launch of an awareness campaign about hereditary cancer, called #invisiblegenes. The campaign encourages genetic testing and counseling.

“Not everybody is getting tested who should be,” says Domchek.

The #invisiblegenes video and social media campaign launched with the help of celebrities like Ryan Seacrest and actress Cobie Smulders, star of television comedy series “How I Met Your Mother” and in the Marvel Cinematic Universe, aims to highlight illnesses that can be prevented or treated with early detection. The campaign features families, especially parents and children, talking about the qualities they inherited or passed along, from personality quirks to body oddities to health risks like BRCA.

It is just the latest of the Basser Center’s efforts to raise awareness about genetic cancer risk. The center has also partnered with more than 1,500 Jewish congregations across the country to distribute posters and fact sheets with details on BRCA gene mutations, which disproportionately impact the Jewish community (due to a phenomenon called the “founder effect,” in which a few specific heritable mutations became concentrated in an Ashkenazi Jewish population that was initially confined to Eastern Europe). The center also works to reach individuals and families around the world, providing education and information via webinars, live seminars, and shareable messages on social media channels to help every person with or at risk for a BRCA mutation make informed choices.

“Tonight, we’re asking you to take the courage to look at your genes,” Mindy told the crowd at the Jean Bash. “Check your history; uncover your risk and ask others to do the same.”

Clinical Context

When getting tested for BRCA mutations, it is vital to undergo that testing in a context where counseling and follow-up care are available and accessible. To that end, the Basser Center also offers remote cancer genetic services for at-risk patients. Using real-time videoconferencing in community practices, Penn’s genetic counselors are able to remotely screen and counsel patients who would otherwise not be able to utilize these services at their current location. But the effort to improve patients’ access to appropriate testing in the context of care does not stop there. A multi-institution collaborative team including Penn’s Basser Center, Memorial Sloan-Kettering Cancer Center, and Dana Farber Cancer Center, recently launched the BRCA Founder Outreach (BFOR) study to find new ways to integrate genetic testing into comprehensive medical care.

The BFOR study launched in January 2018, offering genetic testing at no cost to a total of 4,000 participants of high-risk Ashkenazi Jewish descent, age 25 or older in four US cities—New York, Philadelphia, Los Angeles and Boston. The test will be taken in consultation with a patient’s primary care physician or gynecologist, and thus will combine direct-to-consumer genetic testing with the guidance of a physician to discuss the results.



In general, Basser Center experts recommend BRCA testing for both men and women whose family history includes cancer clusters or people of Ashkenazi Jewish descent with a family history of breast, ovarian, pancreatic cancer or high grade prostate cancer.

“The ultimate goal is determining how this testing and care would actually get done in the long run,” Domchek says. “When we talk about improving population screening, it only works if physicians are engaged. Patients want to know whether their doctors think they should do it.”

at Penn for BRCA-related breast cancer over the last year, and a cousin. A fourth sister tested negative for the BRCA mutation. The three BRCA-positive sisters all feel a connection with Domchek, who takes time to answer every question they have about their follow-up care and about ongoing research on BRCA that could benefit their children. She also connects with them on a personal level; Domchek, Temple, and Schmidt are all moms of boys, sharing tips about raising young men and seeing them through the college application process.

The sisters also find their shared experience keeps them close and keeps them healthy. They occasionally go to appointments together, but more often call and text each other afterward, providing each other with a built-in support system. It's sometimes fun and friendly ("Have you seen her [Domchek's] boots? How does someone with so

Counseling women through personal decisions about preventive surgery is part of the mission of the Basser Center—and so is the quest for better alternatives for effective cancer prevention.

much on her plate find time to have great shoes?") and sometimes plainly health-focused ("Are you taking your calcium?" "Oh no, I need to get on that!"). Far from considering their situation tragic or trying, sisters Temple, Schmidt, and Matos all maintain a positive outlook, bolstered by one another and by their religious faith. "We are all happy people, doing well," Temple says. "We stick together and we're always after each other to take good care of our health."

For Domchek, treating patient-families like theirs is part of a unique style of care at the Basser Center. It feels, she says, as if her practice hearkens back to old-style family physicians who saw multiple generations of patients. "Sisters come to clinic together, or a mom and a daughter," she says. "We're in it for the long term with families. We're with these women through dating, marriage, and children. It's a true privilege that happens so rarely in medicine."

Yet that's just one part of Domchek's typical day, which veers from the clinic where she sees patients to overseeing the Basser Center's broad mission and slate of activities, from the lab bench to the clinic to educational outreach in at-risk communities.

Domchek's own genetics research, for decades, has focused on BRCA mutations and their clinical implications. For most of her career, though, treating patients like Laura Temple and her sisters who had a BRCA-associated cancer, the course of cancer treatment itself wasn't much different than any other type. The BRCA mutation was a marker of sus-

ceptibility and of prognosis—but it had limited direct bearing on standard treatment options.

In the years since the establishment of the Basser Center, thanks in part to the center's research on the biology of BRCA-associated disease, that picture is beginning to change.

Repair, Interrupted

In its most fundamental mechanisms, cancer arises from our own biology—our cells' ability to repair errors, to replace aging cells by creating new cells, to utilize astonishing feats like building new blood vessels and repairing wounds. Cancer cells hijack our innate and life-sustaining biology. In the case of the BRCA genes, the healthy, life-sustaining purpose when the genes work correctly is protection and restoration.

"For BRCA, the important thing to remember is that it is a protein involved in DNA repair," says Roger Greenberg, MD, PhD, the Basser Center's director of basic science research and a professor of Cancer Biology. "When a cell acquires damage to the DNA, it elicits a very complex and multilayered response that comes in and repairs the DNA to maintain the fidelity of our genome." In the absence of two working copies of the BRCA genes, DNA left is vulnerable to additional mutations and changes that eventually can lead to cancer.

In recent years, a growing understanding of how the BRCA genes function and dysfunction in DNA repair has begun to yield new strategies for treatment. Nathanson's collaborative medical genetics research, for example, has identified different specific types of errors on mutated BRCA genes that confer greater risks of certain cancers, helping to inform risk assessment and prevention strategies. Greenberg's basic science lab, meanwhile, is working to understand how BRCA-associated complexes of proteins coordinate to accomplish DNA repair, how these mechanisms are involved in a tumor's responses or resistance to chemotherapy, and even how chemotherapy and the body's immune response work in tandem to kill off cancer cells with damaged DNA.

"I think that's a major question in the field," says Greenberg. "How does the cell handle this catastrophic loss of DNA repair function in the context of *BRCA1* and *BRCA2* deficiency?"

One answer to that question that researchers already know is that cells with mutated BRCA genes rely on other proteins and mechanisms for cellular repair. One of the most important of these repair proteins is called PARP (poly ADP-ribose polymerase). In cancer cells that have mutated BRCA genes, drugs that interfere with PARP-related repair of DNA can push the DNA error rate in the cell over a cliff. The cells may soon be so full of errors that they die. These PARP inhibitor drugs are a form of medicine that uses a tumor's own biological vulnerability to kill it.

The first such PARP inhibitor, olaparib, was approved in December 2014, following Penn-led Phase II clinical trials, and two other drugs in the class have been approved since. These novel medications have transformed ovarian cancer treatment, especially since this cancer is often discovered late



Sisters Jen Schmidt, Laura Temple, Sarah Matos, and Kathy Kilby learned that a *BRCA2* mutation ran in their family a few months after losing their mother to ovarian cancer. Today, three of the sisters have tested positive for the mutation and are breast cancer survivors.

and until recently has had few options. The Basser Center also had significant involvement in a seminal study in *BRCA1/2*-associated metastatic breast cancer patients showing improved outcomes with olaparib compared to chemotherapy, leading to the first FDA approval of a drug specifically for *BRCA*-related breast cancer, in January 2018.

Studies of PARP inhibitors in prostate cancer and pancreatic cancer are underway. Other ongoing avenues of research at the Basser Center that aim to improve the usefulness of PARP inhibitors that are already approved include efforts to understand why some *BRCA*-related tumors do not respond to the drugs, and why most tumors develop resistance. Nathanson is investigating the impact of tumor genomics on these issues. Specifically, she has shown that *BRCA*-related tumors look very different if they lose the second copy of *BRCA* than if one copy still works correctly. She has shown that this has significant implications for prognosis. “Understanding the mechanisms by which *BRCA* tumors develop will help us understand both primary and acquired resistance,” Nathanson says. Domchek and others are still learning about how to use these drugs and how best to combine them with other drugs.

It turns out that PARP inhibitors might have broad implications for cancer treatment. “We’ve already seen that knowl-

edge about PARP inhibitors has translated more broadly to ovarian cancer, and we hope to find groups within other tumor types,” Domchek says. The study of inherited *BRCA* gene mutations has opened the door; there are almost certainly other ways cancers can develop to the point where there are failures in the DNA repair process in which *BRCA* proteins are normally active. “The more you understand how cells respond to damage,” Domchek says, “the broader the implications might be.”

A Global Hub

The Basser Center’s focus on discoveries with PARP inhibitors is no coincidence; it has been the result of a concerted effort to make discoveries in a promising area—and that owes a lot to the influence of Mindy and Jon Gray and their active role in partnering with Basser Center leaders. Mindy applies her marketing savvy and sophistication as a philanthropic leader to forge connections that extend the center’s impact, while Jon complements her approach with his business-minded focus on getting results. Their influence includes philanthropic engagement, such as co-chairing the biennial designer-bluejean-attired “Basser Jean Bash” fundraisers that, between 2015 and 2017, have raised more than \$15 million for the center. But it is not limited to that. “In



Mindy and Jon Gray at the biennial Basser Jean Bash fundraising event.

work, your greatest success happens when you identify something you believe in passionately, hire the right people, and throw your resources behind it,” Jon explains. “Philanthropy, and our work with the Basser Center, is a bit like an investment portfolio in that way. We have a very active dialogue with Penn, engaging with the experts to focus more on really promising research as opposed to sprinkling things around. In this, and in Mindy’s work with the team on social media and awareness outreach, we have a true sense of partnership.”

That partnership comes with the knowledge that helping families with BRCA mutations, like any great challenge in science or medicine, is a global effort, with challenges that can only be solved through the cooperation of the best and the brightest around the world.

To that end, in 2013, Mindy’s sister Shari (who is also a Penn graduate), and her husband Len Potter, established and permanently endowed the Basser Global Prize initiative at the center. The annual \$100,000 prize honors a visionary scientist whose *BRCA1/2*-related research has led to improvements in clinical care. The grant is unrestricted. “Researchers spend too much time writing grant proposals and not enough time in their labs,” explains Len. “Sometimes private philanthropy can be a better means for financing new ideas. This prize acknowledges the great things a scientist has done, but gives them unrestricted money they can apply to the research closest to their heart.”

Prizes have been awarded to Alan Ashworth, a leader of UCSF’s cancer center who has been instrumental in the development of PARP inhibitors and in the discovery of the *BRCA2* gene; University of Washington’s Mary-Claire King; David Livingston, of Harvard’s Dana Farber Cancer Institute; and Steven Narod, director of the Familial Breast Cancer Research Unit at the University of Toronto and a world leader in breast and ovarian cancer genetics. This year’s winner is Ashok Venkitaraman, MBBS, PhD, of the University of Cambridge.

At an annual scientific symposium hosted at the Basser Center to bring BRCA researchers and clinicians together, the Basser Global Prize winner each year is invited to deliver the keynote address. Prize winners also participate on a panel discussion of BRCA that is webcast live for patients and families affected by BRCA mutations to learn about the newest developments. “Penn has become a global center for immunotherapy and cancer research,” explains Shari, “in part because it’s willing to share what it does and be part of larger, worldwide initiative.”

In the same vein, the Grays have asked that Basser Center funds flow to research both within Penn Medicine and to outside, collaborative institutions as well. They donated \$5 million in 2013 for the Basser External Research Grant Program, a program for research projects aimed at advancing the care of people living with *BRCA1/2* mutations. External grants are rare among academic institutions. “It is particularly unusual for a large institution to open its doors to its competitors,” says Mindy. “Susan is a leader who is ego-free and fully believes in the importance of collaboration.”

For the Penn team, global collaboration on BRCA research is a natural fit. Penn was a founding member of CIMBA (Consortium of Investigators of Modifiers of *BRCA1/2*) which has analyzed more than 45,000 mutation carriers around the world to investigate “modifier genes”—changes in genes other than *BRCA1/2* which may impact the likelihood that a particular individual will develop breast cancer. Penn is also part of ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles). With its vast collection of genetic samples from BRCA-positive patients who opted to participate in research since the 1990s, Penn is the largest single-institution U.S. contributor of samples to these key international efforts.

Decisions that Cut Deep

Susan Domchek was the expert sounding board for Sarah Matos after she tested positive for the *BRCA2* mutation, in addition to her sisters Laura and Jen and the Basser Center’s genetic counselors. They talked about options.

Matos, recalling her mother’s suffering with ovarian cancer, which remains difficult to detect early and is often lethal when detected late, decided to remove her ovaries and fallopian tubes. “I was 49 at the time, and I knew I wasn’t going to have any more children, so it was not a hard choice for me,” Matos says. Plus, her sisters had already gone

through the procedure after their breast cancer treatments several years earlier. The surgery can reduce risk of BRCA-related ovarian cancer by about 90 percent and breast cancer by half.

But when it came to removing her breasts, Matos waited. Although Domchek advised her that prophylactic mastectomy can reduce risk of BRCA-related breast cancer by 95 percent, Matos reasoned that regular mammograms and MRI could catch breast cancer early. That's exactly what happened. Matos had a mastectomy then, as part of her treatment. Her two BRCA-positive, cancer-survivor sisters were her experienced support network during treatment and remain so now that she is in remission.

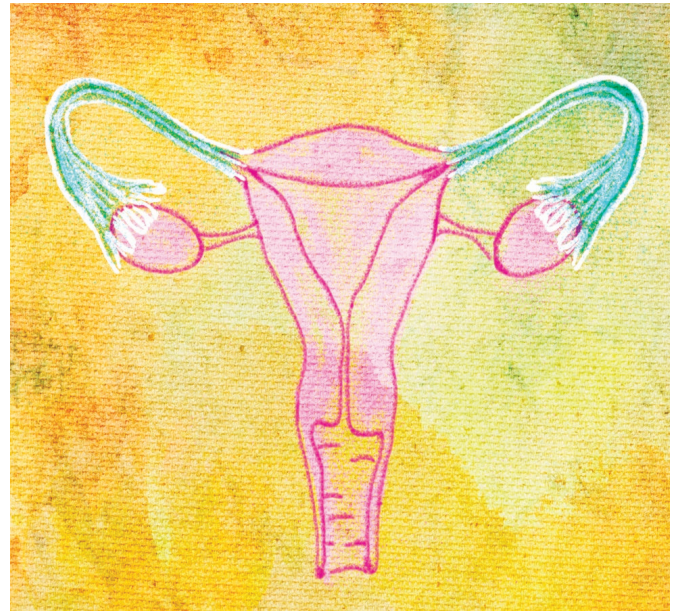
Because BRCA mutations are hereditary, all three sisters know that similar questions about preventive surgeries could lie ahead for some of their own children and future generations beyond. A naturally optimistic person, Matos doesn't spend a lot of time thinking about that. "But when I do think about it," she says, "it is a worry. I have four girls. It's kind of a heavy thing and something they're each going to have to make a decision about." She believes that her two oldest daughters, one 24 and newly married, one 22, will be proactive and get tested for the BRCA mutation at the earliest recommended age, 25. They have already discussed it with their doctors. It's not always easy, but it is part of the fabric of life for families like theirs. Matos's youngest sister, Jen Schmidt, keeps it light, but still top of mind, with her teenage sons, half-scolding them, "You might have that gene so you have to wear your sunscreen!"

Each patient's decision about preventive surgeries for BRCA-related mutations is inevitably a personal one. As effective as these surgeries are in reducing risk, they are serious procedures and they come with trade-offs, especially for younger women. Premenopausal women must weigh their

A growing body of research supports the idea that ovarian cancer in BRCA mutation carriers (and probably most women) originates in the fallopian tube and then migrates to the ovary.

plans for fertility and the timing of childbearing into these choices and also consider that removal of the ovaries will induce menopause virtually overnight—instead of a gradual, five-to-seven year process. Because this surgically induced menopause is so sudden, its uncomfortable symptoms can be severe. Long-term, this early menopause increases risk of heart disease and decreases bone density. Hormone replacement therapy is an option that can be discussed.

Counseling women through these personal decisions is part of the mission of the Basser Center—and so is the quest for better alternatives for effective cancer prevention. "What we want is a better choice for women," Domchek says.



Rethinking an Afterthought

One of the promising alternatives that may lie ahead is the possibility of removing only the fallopian tubes, while preserving ovaries until after menopause.

Historically, pathologists only examined the ovaries removed during cancer surgery because the tumors there were an obvious problem, notes Ronny Drapkin, MD, PhD, a professor of Pathology and director of the Penn Ovarian Cancer Research Center and of gynecologic cancer research at the Basser Center. "The fallopian tube was an afterthought," Drapkin says. Tubes were removed along with ovaries simply because that was convenient to surgeons.

Yet scientists never actually found reproducible evidence for precancerous lesions in the ovaries, despite years of intent examination, Drapkin notes. Around the early-mid 2000s, pathologists began to examine tissues from BRCA-positive patients who had undergone prophylactic surgery, and, at last, a few papers noted abnormal or precancerous cells. But the precancerous cells were not in the ovaries. They were in fallopian tubes.

Then a young faculty member at Dana Farber, Drapkin worked with his former clinical mentor at the Brigham and Women's Hospital, pathologist Christopher Crum, to thoroughly examine every bit of these tissues. "That's when it hit us," says Drapkin. "Oh, my. The fimbria, the end of the fallopian tube that fans out over the ovary, it has all the precursors, dysplastic cells that everybody has been looking for. It's all there."

A growing body of research since that time supports the idea that ovarian cancer in BRCA mutation carriers (and probably most women) originates in the fallopian tube and then migrates to the ovary. This is called a "seed and soil" hypothesis—the fallopian tube may be where the seed begins, but the ovary has the "soil" (growth factors and hormones) that allows the cancer to flourish.

Drapkin and his colleagues have created sophisticated animal models and conducted comprehensive genomic studies on human tissues showing that indeed, the fallopian tube's precursor cells and the ovarian tumors are the same. The latest such study, published in *Nature Communications* in

Research at the Bassett Center is focused on finding better solutions to prevent cancer, including some that do not involve going under the knife.

October 2017, provides genomic evidence that the most common form of ovarian cancer, high-grade serous carcinoma, can trace its origins directly to tumor cells that can be found in fallopian tubes an average of 6.5 years before ovarian cancer begins to grow.

Today, there are already a few clinical practice changes that reflect the general acceptance of this model for ovarian cancer. The American Board of Obstetrics and Gynecology now recommends that even women who don't have any elevated risk for ovarian cancer get their tubes removed if they are undergoing a hysterectomy for any reason, such as fibroids or prolapse. When it comes to young women with BRCA mutations, some doctors are already having conversations about preserving ovaries until after menopause and removing only tubes, though there is a risk that a few cancerous cells might already have left the tube to seed the ovary.

Removing both tubes and ovaries is still standard of care best supported by clinical evidence for women who opt for the surgery, but new long-term studies may one day change that standard. In 2017, Penn joined fifteen other institutions across the country on a twenty-five year prospective trial to study the impact on quality of life as well as cancer risk in women who have both the ovaries and fallopian tubes surgically removed at the same time, compared to women who initially have their tubes alone removed, followed by removal of the ovaries at a later date, usually after menopause.



Photo by Peggy Peterson

For Domchek, finding discoveries in the spaces where top experts' skills overlap is the only way to make a vision as large as that of the Bassett Center a reality. "In the medical sciences, people talk a lot about service teams and collaboration," she says, "but truly it takes different people with tremendously different expertise, and getting all of these people to collaborate and talk to each other. We're really fortunate to be at Penn, where that happens." (Bassett Center leadership team, L-R: Domchek; Beth Stearman, administrative director; Ronny Drapkin, MD, PhD, director of gynecologic cancer research; Katherine Nathanson, MD, director of genetics; Roger Greenberg, MD, PhD, director of basic science research)



Towards A “Smallpox” Vaccine for Cancer

The preventive surgeries that are standard of care today already dramatically reduce the risk of cancer in women with BRCA mutations—but, although the surgery can save and dramatically extend women’s lives, it is still not an ideal solution. Research at the Basser Center is focused on getting closer to those ideal solutions, including some that may help women avoid cancer without going under the knife.

“We want to develop what is essentially a smallpox vaccine to prevent cancer,” says Robert Vonderheide, MD, DPhil, director of the Abramson Cancer Center. “But we won’t be targeting a virus. We’ll be targeting a genetic mutation.”

Vonderheide and a team of Basser Center colleagues are leading vaccine-based trials for the prevention of cancers associated with BRCA mutations. They are focusing on human telomerase (hTERT), an enzyme that is crucial for the survival of cancer cells—so much so that its production is overactive in about 90 percent of human cancers, including *BRCA1*- and *BRCA2*-related cancers. Laboratory studies at Penn have shown that vaccinating against telomerase induces an immune response that attacks and kills cancer. For clinical testing now underway, the vaccine has been tweaked with other molecules and a special method of enhancing its delivery, in order to maximize its effectiveness.

Patients in remission after treatment for any one of multiple forms of cancer, including, breast, ovarian, and pancreatic, are now enrolled in a first-in-human Phase I trial at Penn. So far, the clinical trial data indicate that the vaccine is safe, and results on the participants’ immune response to the vaccine are forthcoming. Testing the telomerase vaccine approach in patients who are considered to be at high risk of a cancer relapse is a first step toward its potential use to prevent novel cancers in healthy people at high risk, such as BRCA mutation carriers.

“I believe we are entering an era of using the immune system to prevent cancer,” Vonderheide says. “This is a watershed moment in cancer research.”

Partnering with the Right People

The torrent of progress in immunological approaches to cancer has unexpectedly brought together the previously disparate professional efforts of Vonderheide and Domchek, who are married to one another and have raised their sons into teenagers in the years since the pair was recruited to Penn more than a decade ago. “I was always interested in genetics, he was always in immunology, and all of a sudden they intersected,” Domchek says. “It wasn’t planned but it certainly has been an interesting development that the big circles in our Venn diagram are overlapping in this way that can really make a difference.”

It was a stroke of fortune, too, that Domchek came to work with Mindy and Jon Gray to bring the Basser Center to life. The day of Jon’s 2011 epiphany, coming in from a run to interrupt Mindy’s breakfast with the idea to start such a center, it was not a foregone conclusion that the center would be at Penn. But their Google searches on BRCA research kept turning up Domchek, so they cold-called her. When Domchek recalls the conversation today, it is with some embarrassment: She didn’t know who Jon and Mindy were, how important they would turn out to be in her life’s work. Without any fanfare, speaking to them as she would to any family affected by BRCA, she impressed them with her knowledge and enthusiasm. She talked about the decades of research at Penn on BRCA that had established so much of our basic knowledge about the gene mutations and how they confer risk; that had examined prophylactic surgery and helped demonstrate the benefits in cancer risk reduction and improved survival, along with describing the side effects, laying the groundwork for how clinicians worldwide work with BRCA-positive patients today; that had performed early studies of PARP inhibitors and continued through demonstrating the effectiveness of these drugs; that was a key player in global collaborative efforts; and that was poised to draw on its history to continue pushing further to help more families with hereditary cancer risk, in more places, for many years to come.

“She gave us over an hour of her time, without knowing anything about us,” says Jon. “She was measured and passionate. And she was at Penn, our alma mater. It seemed to be fate.”

“Fate and Faith,” says Mindy. “They are the guiding themes of our lives.” ▢

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By Steve Graff

The first-of-its-kind FDA approval of an immune cell therapy for cancer was big news on Penn's campus. It marked the culmination of a chapter of discovery, collaboration, and spectacular feats of surviving once-deadly cancers. And it's the start of much more.

On the morning of August 30, 2017, the U.S. Food and Drug Administration announced what was called an "historic action": A University of Pennsylvania-developed personalized cellular therapy was approved for the treatment of advanced acute lymphoblastic leukemia (ALL) in children and young adults. Hours later, the newly minted director of the Abramson Cancer Center (ACC), Robert Vonderheide, MD, DPhil, found himself atop a coffee stand in the lobby of the Perelman Center for Advanced Medicine, looking out over a crowd numbering in the thousands that had gathered to celebrate, all beaming with pride and joy.

Carl June, MD, the pioneer who led Penn's charge into this new cancer frontier, had just arrived.

"This is absolutely an amazing day," Vonderheide said. "There's just one thing I want to tell you...the Abramson Cancer Center is on fire."

Before that bright crowd, Vonderheide didn't have to explain much.

They knew that it was the first time the FDA had approved a therapy based on gene-transfer technology that used a viral vector to insert genetic material into a T cell. It was the first time the agency had approved a personalized therapy that used a modified version of a patient's own cells as a treatment. And it was a major moment in the unfolding renaissance of exciting developments of therapies that empower the body's immune system to fight cancer. They had seen the lives saved in their own hospital during the early, experimental days of using the treatment, and they knew what its approval signified, for more lives in more places.

The Radical Idea

Even 10 years ago, the moment would have been considered a pipe dream.

The immunotherapy field was still relatively small, with few research groups around the world investigating ways to manipulate the immune system's T cells to fight disease. Pharmaceutical companies had little interest. Funding was scarce. And people from other biomedical fields largely viewed as a low priority.

None of this seemed to discourage June, an immunologist who had been working with modified T cells to develop experimental HIV therapies since the mid-1980s. By the time he and his then-postdoctoral researcher Bruce Levine, PhD, now the Barbara and Edward Netter Professor of Cancer Gene Therapy in the department of Pathology and Laboratory Medicine, landed at Penn in 1999, they had cracked the code on how to get T cells to grow outside the body, and safely infused a small group of HIV patients with first-generation chimeric antigen receptor (CAR) T cells



Robert Vonderheide, MD, DPhil and Carl June, MD

that enhanced their immune function. Blood cancers would be next.

“People advised me to think carefully about working with Carl because they said the work he was doing was high-risk and unlikely to be successful,” said Michael Milone, MD, PhD, GME’02, an associate professor of Pathology and Laboratory Medicine, who joined June’s lab in 2003 as a postdoc and helped develop a CAR T cell designed to find the CD19 protein expressed on B cells. “Happy to prove them wrong!”

“Spectacular” Results

By 2009, the team, which by then included David Porter, MD, director of Blood and Marrow Transplantation in the ACC, was ready for human testing of that CAR T cell, which became known as CART19 and later, as CTL019. The National Institutes of Health had declined to fund the work several times over the years, but help from private funders allowed the researchers to now conduct a small trial—just three patients. Out of options to treat aggressive chronic lymphocytic leukemia (CLL), these three Penn patient-pioneers said yes to trying one more thing.

A billion or so of their T cells were removed, reprogrammed with a modified, harmless HIV virus and taught to seek out that CD19 protein on cancer cells, and then infused back into their bodies to multiply and attack.

A year later, results from that trial—two of the three patients experienced complete remissions of their disease, and a third had a partial response—published in the *New England Journal of Medicine* and *Science Translational Medicine* grabbed people’s attention. Headlines the next day read “Huge”

Results Raise Hope for Cancer Breakthrough” and “Immune System, Loaded with Remade T-cells, Vanquishes Cancer.” Calls and emails from more than 5,000 patients and desperate family members poured in to the research team, asking if the therapy was ready to help them, too. And the news caught the pharmaceutical industry’s eye.

By 2012, June and his team, in close partnership with the Center for Technology Transfer (now the Penn Center for Innovation), formed an alliance with global giant Novartis to accelerate research, development, and commercialization of CAR therapies. Trials in adults and pediatric patients from Children’s Hospital of Philadelphia (CHOP) with another blood cancer known as acute lymphoblastic leukemia (ALL) also got underway, with Stephan Grupp, MD, PhD, director of the Cancer Immunotherapy Frontier Program at CHOP, and the Novotny Professor of Pediatrics at the Perelman School of Medicine, taking the clinical trial helm at CHOP. Noelle Frey, MD, an assistant professor of Hematology-Oncology at Penn, joined Porter to lead the adult trials.

“These patients in general had a life expectancy of three months, and 90 percent of them had complete remission,” June said. “It was just spectacular.”

Success of the pediatric trial led to a global trial for advanced ALL that began in 2015 at 25 centers around the world. The results were equally spectacular: Of 68 children and young adults, 52 patients achieved complete remission.

Verge of Approval

Six months after researchers published those results, in July 2017, Tom Whitehead, the father of Emily Whitehead, Grupp’s patient at CHOP and the first pediatric patient to receive CTL019, stood before an FDA panel in Washington, D.C., imploring them to recommend the drug’s approval. Emily, who was near death on her seventh birthday, has since been cancer free for over five years. “We believe that when this treatment is approved, it will save thousands of children’s lives around the world,” he told them.

The committee reviewed the data and said yes, in a unanimous vote. Forty-nine days later, the therapy, marketed by Novartis as Kymriah, officially became approved. Now, patients with ALL up to age 25 who have exhausted all other options can receive it at roughly 30 centers across the country, including Penn and CHOP. That’s about 600 patients per year. In the aftermath of the approval, questions about costs of the therapy remained a part of the public discussion. But on August 30, the focus was on celebration of this historic moment.

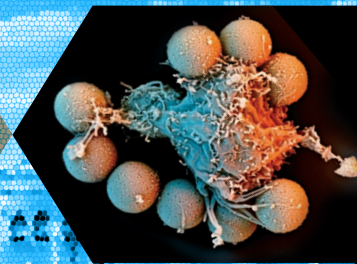
Cell-ebriation

Back at Penn’s Perelman Center, June was now walking through the crowd like an esteemed conductor heading to his orchestra. Vonderheide stepped down from the coffee stand, and June took his place. He kept it short, too.

“Today, the cancer world has changed forever,” he said. “And I will never forget it.”

Cheers erupted from the crowd. □

Pioneers of Cellacon Valley



Talk to immunotherapy researchers around Penn's campus, and they'll likely say the same thing: It's just getting started.

"We are driven by the desire to make these types of therapies as widely available and applicable as possible," said Robert Vonderheide, MD, DPhil, director of the Abramson Cancer Center. "We're looking justifiably at ramping up the scale of this to never before seen dimensions because it's working...it's time for these therapies to become mainstay."

Getting to this point did not happen quickly or alone, of course. It took time and visionary funders, not to mention an infrastructure buildup and the right industry partner to move the first chimeric antigen receptor (CAR) T cell therapy from the bench to the clinic.

"Much of the [investments in the therapy] were unheard of when we started...15 to 20 years ago," said Kevin Mahoney, executive vice president and chief administrative officer for the University of Pennsylvania Health System. "We were ahead of the curve."

Support from the Abramson family and Barbara and Edward Netter's foundation, Alliance for Cancer Gene Therapy, as well as the Leukemia & Lymphoma Society, helped get Carl June's cell therapy lab and production facility up and running in the early 2000s and his first CAR clinical trial open in 2010.

"When the first patient results were published in the summer of 2011 we were inundated almost immediately by expressions of extreme interest from the biopharmaceutical industry, the venture capital community and independent entrepreneurs," said John Swartley, associate vice provost for research and managing director of the Penn Center for Innovation.

As a result, within a decade, the early philanthropic commitments had paid off. Penn had formed an exclusive licensing agreement with the global pharmaceutical company Novartis to ramp up CAR research and development. Next came the Penn-Novartis Center for Advanced Cellular Therapeutics, a state-of-the-art, 30,000- square foot facility above the Perelman Center for Advanced Medicine, that upped Penn's capacity to investigate new uses for the technology, conduct clinical trials, and hire researchers.

That alliance has undoubtedly taken the institution into a new era of commercialization for cellular therapies, and solidified its position at the center of "Cellacon Valley," A nickname coined at Penn for the bustling, cell and gene therapy hub that is Philadelphia.

It is a position not sustained by just one industry partnership, but by the university's capacity to forge multiple connections

and collaborations to develop discoveries into commercial therapies.

"The best way for us to make connections with the [biotech and pharmaceutical companies] are with assets that we excel at," Mahoney said. "And cell gene therapy is something the Children's Hospital of Philadelphia and Penn are international leaders in."

Collaborations with other biotech companies researching cellular and gene therapies in cancer and other diseases, such as Celgene and Biogen, have since materialized, as did the partnership with the two-year-old Parker Institute for Cancer Immunotherapy. The \$250 million effort brings together scientists from six other medical schools and cancer centers, as well as industry partners. It's an unprecedented move from the inventor of the music-sharing program Napster, with an ambitious, underlying goal: expedite discoveries into the clinic.

"These teams enable us to work outside our own comfort zone, and tackle problems we wouldn't otherwise do," said June, who serves as the director of the Parker Institute at Penn. "It allows us to recruit new scientists and promote the careers of some junior scientists and faculty. It's early on, but so far, it's enabling some interesting trials that would not have been here otherwise."

Altogether, Penn now has over 40 clinical trials investigating cellular therapies in a host of both blood and solid cancers and other diseases. And trials are what attract outsiders—"good, human clinical data," Mahoney said—making them a priority area for investment and growth in the eyes of Penn Medicine leadership.

So is sprouting new companies. Penn's entrepreneurial ecosystem—shaped by the Penn Center for Innovation and its UPstart program—has helped both senior and junior faculty navigate the waters of business development and jumpstart their ventures. June's company, Tmunity, which focuses on different CAR T cells and other engineered T cell therapies, and CARMA, from Saar Gill, MD, PhD, an assistant professor of Hematology-Oncology, which puts CARs into another type of immune cells, macrophages, are just two examples.

"The explosion of commercial interest in cell and gene therapy over the last decade has been driven in large part by the monumental scientific and clinical discoveries and developments made by groundbreaking faculty leaders at Penn such as Carl June and Jim Wilson," Swartley said.

Patient Number One

After Alison Loren, MD, delivered the news to Bill Ludwig that his body was free of leukemia, he lay down in his bed in the Hospital of the University of Pennsylvania, looked around the room, and let the doctor's words sink in.

After an hour, he walked out to the nurses' station. "Has Dr. Loren been on this floor this morning?" he asked. She had checked in with them on her way to his room, the nurses said. "She didn't see you?" they asked.

"Oh yeah, she saw me," he said. "I was just making sure that I remembered it correctly. Because I could be hallucinating."

But this time, he wasn't. After weeks of chaos—fevers and chills, hallucinations, legs swelled up to three times their size, he had ended up in the intensive care unit. But now his oncologist, Loren, delivered this good news. It was the chimeric antigen receptor (CAR) T cells that had sent his immune system into cataclysmic overdrive, and they had been doing their job all along: finding his B-cell chronic lymphocytic leukemia (CLL) and destroying it. Five and a half pounds of cancer were wiped out in less than a month.

Ludwig would forever be known as the first person to be successfully treated with a cellular therapy designed to hunt down and kill cancer cells with his own immune system.

"I'm looking for [extending life by] a day, a week, or a month, and here they are telling me I don't have cancer," Ludwig said. "It was just like someone told you, 'You won the lottery.'"

It had been an arduous, nearly 10-year path to get to this unprecedented result. Diagnosed with CLL in early 2001, Ludwig spent the better part of that decade undergoing round after round of different chemotherapies that ultimately stopped working. He didn't qualify for a bone marrow transplant. And a clinical trial at the National Institutes of Health in Bethesda, Md., proved fruitless for him. In early 2010, he found himself back at HUP under Loren's care, and seemingly out of options.

That's when she brought up an experimental therapy from the team led by Carl June.

"[Penn] had kept me alive for nine years. They needed someone to go into a clinical trial," Ludwig said. "Why not?"

He received his first infusion on Tuesday, Aug. 3, 2010. Two others followed that week. Then the chaos ensued that sent him to intensive care. But initially, no one was sure what was happening to him.

"This was brand new territory and we didn't know what to expect," said David Porter, MD, director of Blood and Marrow Transplantation in the Abramson Cancer Center, and a clinical leader on the CAR team. "And he was getting sicker, and I will freely admit that I was convinced he had pneumonia."

Researchers would later discover that the billion engineered T cells placed back in Ludwig's body grew to a trillion and went on a war path to kill his B cells. All the symptoms his



body had experienced were the casualties from that all-out attack. It's called cytokine release syndrome.

"The elation when he started getting better, and you realize that his leukemia is rapidly disappearing is incredible," Porter said. "You start becoming a little more convinced that the illness period really did have something to do with the T cells, and it wasn't an infection."

Not one, but two bone marrow biopsies showed no sign of cancer cells, and his lymph nodes now appeared normal sized on an X-ray. This was the news that Loren delivered in the aftermath of Ludwig's three-week ordeal.

Back from the nurses' station, Ludwig waited for his wife, Darla. "She walked in and I told her," said Ludwig, his voice cracking. "We just hugged each other. And we both cried."

The next day, they left the hospital.

That was seven and a half years ago. Ludwig remains in remission and in good health, enjoying each day with Darla, their kids, and their kids' kids, traveling around the country in their RV or just being at home.

"I know it's a cliché, but everything's precious," said Ludwig, now 72 and retired from his career as a corrections officer. "I just keep thinking of the things that I would have missed... seeing granddaughters in college and watching grandsons grow up."

There's profound gratitude and emotion in Ludwig's voice when he talks of his experience at Penn—and everything that has unfolded with the "living drug" since.

After Ludwig, over 330 more adults (and counting) would go onto be treated with CTL019 therapy at Penn. His trial

Continues on next page



also paved the way for the clinical trials in children and young adults with acute lymphoblastic leukemia (ALL) that ultimately led to the therapy's approval.

In a way, he went along on that journey.

He remembers crying—"like a baby"—in his living room watching NBC's *Nightly News* when they featured the story of Emily Whitehead, the first child to successfully be treated with CTL019 at the Children's Hospital of Philadelphia. He's thankful to have met Doug Olson, the other patient who had a complete response to the therapy in 2010 and remains well today, and others whose lives were saved or improbably extended by the therapy, when attending a 2013 ceremony where June and his team received the Philadelphia Award.

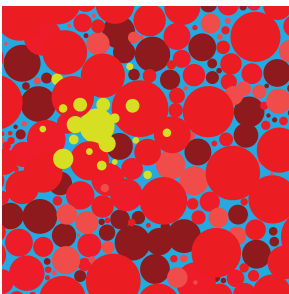
And when he found out the therapy had been approved—via a Facebook post from his daughter—he was overwhelmed with excitement, mostly over what's to come.

"Hopefully there is no end to the cancers that ultimately the immune system will be able to eliminate," Ludwig said. "Let's hope this is the beginning of something large that maybe future generations will take for granted." ▢

The Next Generation

Researchers have only just begun to write the book on immunotherapy and already the pages are filling up fast. Penn's personalized cellular therapy for leukemia is only one of its chapters.

"We have plans in almost any kind of cancer you can think of," said Carl June, MD, director of Penn's Center for Cellular Immunotherapies.



Blood Cancers

The same therapy that proved itself in pediatric and young adult advanced leukemia patients has shown its power in trials for multiple myeloma and non-Hodgkin's lymphoma. In a recent *New England Journal of Medicine* study, a team led by Stephen Schuster, MD, director of the Lymphoma Program, showed that up to 71 percent of adult non-Hodgkin's lymphoma patients who didn't respond to conventional therapies or relapsed had a complete response with the CAR T cells known as CTL019.

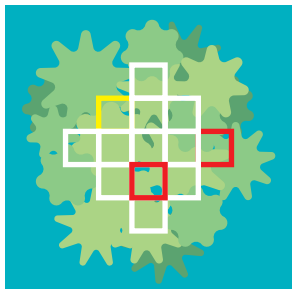
The trajectory is strikingly familiar: powerful data from a Penn trial of patients with otherwise intractable cancers, a U.S. Food and Drug Administration Breakthrough Therapy designation that helped fast-track the leukemia approval, and an equally impressive global trial. This story could very well unfold like the last.



Combined Therapies

Engineered CAR T cells can do wonders in blood cancer patients, but there is still a cadre of people who don't respond. "The idea of combining different approaches with the CAR T cells to help them work better is very logical," said David Porter, MD, director of Blood and Marrow Transplantation. "And early experiences show that it's very promising." In a pilot trial, eight out of 10 patients with chronic lymphocytic leukemia receiving the drug ibrutinib had a complete response after being infused with CAR T cells known as CTL119. The drug, Porter said, makes the T cells more functional and the cancer cells easier to kill.

More combination trials, some with the hot immunotherapy drugs, known as checkpoint inhibitors, are also underway at Penn and Children's Hospital of Philadelphia.



Solid Tumors

The biggest challenge CARs face now is the solid tumor. The so-called tumor microenvironment, the normal cells and blood vessels that surround and feed a tumor, puts up a tough fight that's keeping these engineered cells out of the tumor to do their job.

In a brain tumor trial led by Donald O'Rourke, MD, an associate professor of Neurosurgery, cells called CART-EGFRvIII T cells have made their way to brain tumors—and elicited a few promising responses—but they're triggering an immunosuppressive response that's undermining the approach.

Newer trials for melanoma and triple negative breast cancer have also begun, as has a prostate cancer trial led by Naomi Haas, MD, director of the Abramson Cancer Center's Prostate and Kidney Cancer Program, that targets a prostate-specific membrane antigen—CART-PSMA for short.

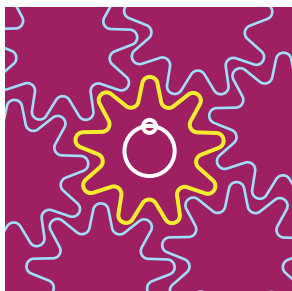


A Different Target, and Epigenetic Approach, for Pancreatic Cancer

An engineered T cell called CAR-meso has shown the most promise in solid tumors. Instead of targeting the proteins found on B cells, CAR-meso goes after mesothelin, an antigen on mesothelial cells that line a lot of the body's cavities and organs. It's also overexpressed in lung, mesothelioma, ovarian, and pancreatic tumors, making it an ideal target for an engineered T cell. Early trials have proven it's up to the task, and now a trio of investigators is pushing it further with a unique genetics approach to better understand why some respond and others don't, under a Stand Up to Cancer grant for pancreatic cancer.

They want to know: Could epigenetic changes in the tumor and T cells be behind the variability in patient response? If so, perhaps existing drugs that target such changes could somehow make the CARs more potent and release the brakes that tumors put on the immune system. Linked to several cancers, epigenetic factors can turn a gene on or off, without changing the underlying DNA sequence. The all-star team is co-led by E. John Wherry, PhD, director of Penn's Institute for Immunology, Shelley L. Berger, PhD, director of Penn's Epigenetics Institute, and June.

"This Stand Up to Cancer grant is bringing together scientists with different expertise and knowledge: Carl works on immunotherapy. I'm an epigenetic scientist. John is a T cell biologist," Berger said. "The advances are amazing when you get people together. The speed of the advance is so much greater"

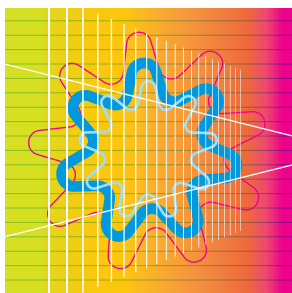


Engineered Macrophages

Another engineered cancer-fighting immune cell—known as CARMA—stands out because it's not a T cell, rather a macrophage, another type of white blood cell known to flock to solid tumors. Saar Gill, MD, PhD, saw that as an opportunity.

"We reasoned a cell that is already predisposed to trafficking into the solid tumor, like the macrophage, might be a good one to genetically engineer and actually make it a cancer killer instead of what it normally does, which is act as an accomplice to help the tumor grow," Gill said.

A study from last year showed it's working, and Gill's lab has spun the technology into a company, CARMA Therapeutics, that aims to get it into solid tumor clinical trials sometime in 2019.



Beyond Cancer

Researchers are also thinking outside the cancer box.

Mouse studies from Michael Milone, MD, PhD, Aimee Payne, MD, PhD, an associate professor of Dermatology, and their colleagues, have shown that chimeric autoantibody receptor, or CAAR, T cells can destroy the rogue immune cells that make antibodies that cause the blistering skin autoimmune disease known as pemphigus vulgaris (PV), while sparing the good ones.

This is an important finding because if they can engineer a CAR T cell to attack rogue immune cells, they can likely make them for other autoimmune diseases and perhaps even for patients who suffer some types of immune rejection after an organ transplant, Milone said. A clinical trial in PV is slated to begin this year.

It will join nearly 240 other clinical trials exploring engineered CAR cell therapies at institutions around the world. So far, at Penn and CHOP, more than 450 patients have been treated with some type of engineered cell therapy.

"There are very few places in the world that have comparable resources to what Penn has in the cellular therapy space," Milone said. "We have a huge team that runs the gamut, from basic science to translational medicine... It's the place to do it with efficiency." □

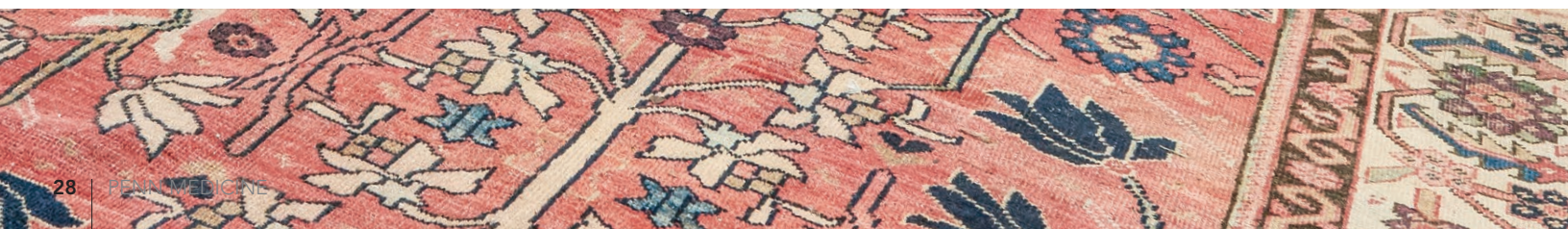
A Vision, Realized

By S.I. Rosenbaum

Photos by Peggy Peterson



Gene therapy to reverse inherited blindness was an outlandish dream in the 1980s when Jean Bennett, MD, PhD, and Albert Maguire, MD, began their collaboration in life and work. Today, it is the first light in a new vista for genetic disease.



To begin with, they shared a brain. It sat between them on in a tray, smelling of fixative agents. They'd already begun cutting into it, and it had flopped open, exposing the hypothalamus.

Jean Bennett and Albert Maguire were both first-year medical students at Harvard, but Bennett already had a doctorate in zoology. Maguire felt he had to make a grand gesture to catch her eye. He took her gloved hand and gently poked her finger right into the bundle of nerves at the rubbery center of the hypothalamus—the pleasure center.

"That's my favorite organ," he murmured.

Instead of recoiling, she wiggled the finger in his grasp. She looked at him.

"It's my *second* favorite organ," she replied.

And that was that.

"As you can tell," she says, "I fell for Al's sense of humor."

"I was especially happy to find out someone else hadn't used that pickup line on her before," he says.

They tell this story, their meet-cute, with relish—swapping punchlines like the long-married couple they are today. After more than 30 years of an extraordinary partnership, Bennett and Maguire have hit a lot of traditional milestones: They have the house, three kids and two dogs. But they've also collaborated in ways few married couples have. The dogs were originally laboratory subjects, and the children grew up listening to their parents talk over experimental medical procedures at the dinner table.

Working in tandem for decades at the Perelman School of Medicine at the University of Pennsylvania, Bennett and Maguire became pioneers in the field of gene therapy—a discipline that was science fiction when they met. In December, they hit a milestone unique to them: The Food and Drug Administration (FDA) approved their treatment for a form of inherited blindness, the first such treatment for a genetic condition ever approved in the U.S.

"By putting our two experiences together and our perspectives on things," Bennett says, "it really propelled us much further than either one of us could go alone."

Seeing Eye to Eye

They were still newlyweds—and still med students—when Maguire asked Bennett the question that would change the course of their lives.

She had told him about her postdoctoral work studying molecular biology. She'd been intrigued by the potential to treat genetic diseases by going to the source—replacing a patient's warped genes with a clean copy. At the time, no such therapy existed, but she could see that it was coming, and she wanted to be ready. That's what had led her to augment her PhD with a medical degree in the first place.

Maguire, meanwhile, in training to become a retinal surgeon, was working with patients who were slowly going blind because they'd inherited flawed copies of a single gene.

Do you think, he asked his wife, that we could develop gene therapy to cure inherited forms of blindness?

Her answer sealed their fate: "Sure," she said.

At the time, neither of them quite realized what a challenge they were taking on. It was "like thinking you wanted to go to the moon in 1950," Maguire says in retrospect.

"We were so naive that it didn't scare us," Bennett says.

Besides the hefty technical challenges ahead of them, they also had to learn to work as a team. Their first attempt at collaboration was rocky: Maguire, who had never worked as a researcher, was frustrated when their work didn't yield immediate results.

"Research requires an extraordinary amount of patience," Bennett says. "But when it comes to surgery he has more patience than anyone I've ever seen."

"I have the ability to concentrate intensely for short periods of time," Maguire says. "She can do that for years."

The Goal in Sight

By the 1990s, Bennett and Maguire had been recruited to Penn's Scheie Eye Institute. All around them, technology was catching up with their ideas: Genes for different forms of inherited blindness were being identified, and scientists were creating transgenic mice with those same mutations, as well as perfecting techniques for inserting genes in viral vectors that could be used to "infect" an animal cell with those genes. At first, the couple experimented on congenitally blind mice. But by coincidence, it turned out that Penn's veterinary school housed a colony of blind dogs.

The human condition equivalent to the dogs' genetic defect is known as Leber's congenital amaurosis (LCA), a severe, progressive inherited disease. People who carry the malformed gene, *RPE65*, are born with poor vision and eventually lose their sight entirely. The effect on the dogs was much the same—and unlike humans, the dogs couldn't use technology to help them get around.

To gauge their impairment, Bennett did a simple test, putting the dog in an obstacle-strewn room and calling it to come. The dogs blundered and stumbled around, unable to see their environment. Bennett felt sorry for them. "Dogs are so visual," she says. "When you saw these blind animals, you wanted to help them and allow them to see a squirrel and run after a squirrel." Instead, the blind dogs seemed listless. "These poor creatures, they would just sit there."

They dove into research but tried not to let their project take over their personal life, limiting the amount they talked about work at home with their kids—who nonetheless learned to roll their eyes when one of their parents slipped up and started discussing retinas at the dinner table.

Maguire initially treated three dogs, injecting a virus into one of their eyes. The virus had been designed something like an M&M: Once inside a cell, its protein shell melted away to leave

only a snippet of DNA that could make the enzyme the dogs' cells couldn't make on their own.

Days after the injection, a lab tech reported the dogs were turning in circles: It seemed like they were trying to look around them with the eye that had been treated. Within weeks, electroretinograms confirmed that the dogs could see. More impressively, when Bennett ran them through the obstacle course again, they were able to navigate it safely and quickly.

It was a successful trial. The only problem was that Bennett and Maguire were having trouble maintaining a proper scientific distance: Both dog lovers, they found their post-surgery subjects hard to resist.

"Once the dog licked my face, wagging its tail—you're done with, it's over," says Maguire.

Adopting a dog who has been part of an experimental gene therapy trial was not easy, they found. "People

were worried about gene transfer," says Bennett. "Is it going to escape the dog, is it getting into the drinking water? ... We really didn't know." They had to do more research to make sure that once the virus got to the dogs' retinas, it stayed there. Armed with their data, they argued their case to the provost.

Venus and Mercury, lab animals no more, ended up going home with them.

"They're the nicest, sweetest animals you can imagine, they're just the sweetest dogs," says Maguire. "I mean, everybody says that about their dogs—but they really are."

Sparkling

More than a decade after Maguire and Bennett treated their first dog, a young woman named Katelyn Corey lay in a hotel room with bandages across her face. Behind the bandages, she was seeing something strange: flashes of light, like little sparks.

Corey had been born with LCA. Her vision had never been great, but she had learned to cope with it, using large-print books, writing with a Sharpie instead of a pencil, color-coordinating her clothes. When she was 15, she and her family sought to enroll in an early phase clinical trial of Bennett and Maguire's gene therapy, but her vision at that time was too good to qualify her for the experimental procedure. By the time she got to college, however, her vision was getting rapidly worse. "I'd adapted to how to take notes, how to study, all those years in high school," she recalls. "But now it wasn't working anymore."

She knew she would eventually become totally blind, and she knew she'd find a way to cope with that too, one way or another. But in 2012, her sophomore year, she decided to give herself six months to find a treatment—a last-ditch effort to save her sight.

She found her way back to Bennett and Maguire. This time, she qualified.

The couple had finally moved to human trials in 2007, after the nearby Children's Hospital of Philadelphia (CHOP) had invested in creating a Center for Cellular and Molecular Therapeutics. The then-head of that center and a professor of Pediatrics at Penn, Katherine High, MD, had knocked on Bennett's lab door one day and asked if she wanted to run a clinical trial to use gene therapy to treat congenital blindness. "I don't think I even called AI to ask him," Bennett recalls. "I just said yes."

Two years later, they injected their first young-adult human volunteer with the viral reagent.

Safety was the utmost priority in human trials. Bennett and Maguire asked themselves, if one of their kids had LCA, would they let them participate? "We both had to answer that affirmatively," she says. To make sure their ethical standards were high, she and Maguire waived any chance of financial gain if the therapy proved successful.

Bennett found herself bonding just as closely with her human subjects as she had with their canine ones. "Each one of them is like family with us," she says. She's visited their homes, watched their



Jean Bennett, MD, PhD

F.M. Kirby Professor of Ophthalmology

Director, Center for Advanced Retinal and Ocular Therapeutics

Studies molecular genetics of inherited retinal diseases

Venus

Swedish Briard Dog

Female, Age 10

Enjoys sitting beside Bennett as she plays the piano



Albert Maguire, MD

Professor of Ophthalmology

Retinal surgeon at Penn and CHOP

Led clinical trials for therapy now known as Luxturna

Mercury

Swedish Briard Dog (puppy to Venus)

Male, Age 8

Enjoys exploring new smells and drinking out of the toilet



Katelyn Corey, now 25, testified before an FDA advisory panel in October 2017. “I can finally live my life the way I want to.”

kids give musical recitals. “I feel so lucky to be able to get to know them and be part of their lives and understand how this has affected them,” she says.

Making the trial participants feel comfortable with her also leads to better science, she adds: Patients who felt connected with her would more readily share their experiences.

Maguire, on the other hand, kept his distance. “I think a huge part of success for the trial was my wife and her connection with the patients in the study,” he says. “But I’m also their doctor, and as a surgeon you have to have this space where I’m not too close to them.”

By the time Corey enrolled, the trials were in Phase III—the last phase before a treatment can be approved by the FDA. (That possibility in sight, High left CHOP and Penn in 2013 to become president of Spark Therapeutics, a new startup company spun out of CHOP, where Bennett, Maguire, and their teams still collaborate.)

Corey was initially randomized into the trial’s control group. A year later, she was finally offered the real gene therapy. When her bandages were removed, she was amazed to find that her sight was better—not just better than it had been before the treatment, but better than it had ever been in her life.

“Things were brighter, sharper,” she says. The world was in color instead of black and white. Outside her hotel window, there was a light she’d thought was the moon; now she realized it was the clock tower in Philadelphia City Hall. Even indoors, there was enough light to see by: “The fact that that light was coming into the hotel room and causing it to be light in there—that was and still is crazy to me,” she says.

A few days later, she turned 21. At a follow-up appointment, Maguire gave her a bottle of Prosecco that he and Bennett had gotten for her.

“Do you think this is a good idea?” Corey asked. She was still on prednisone from the surgery.

Back at the hotel, she and her parents toasted over birthday cake.

Eyes on the Prize

Corey, now 25, testified before an FDA advisory panel in October. “I just want you to know that this was significant to me, significant in the way that I live and plan my life,” she told the regulators. “I can finally live my life the way I want to.”

Also testifying that day was the most famous trial participant, “America’s Got Talent” contestant Christian Guardino. His successful treatment had brought the trial popular attention from new quarters. “Gene therapy has made my world literally so much brighter,” he said. “I’m even able now to walk around freely on stage and perform, and not just stand in one spot.”

Two months later, Bennett got the call: The advisory panel had voted unanimously, and their treatment regimen, now readied by Spark for commercialization and branded as Luxturna, had officially been approved.

She and Maguire were thrilled. Their decades of work had finally paid off. Over a thousand people in the U.S. would have a chance at restoring their vision.

Mere weeks later, Bennett and Maguire already have their sights set on new challenges and questions. If they treat children early enough, can they totally prevent the disease? Do repeated treatments increase the effect? And there are other forms of inherited blindness they want to try treating, forms that will require entirely new methods.

Meanwhile, at home, they’re just a normal couple with hobbies, some shared, some separate. She plays the piano; he paints portraits of cows. And they keep bees. They have five hives.

Keeping busy with their own pursuits, Bennett and Maguire also see the broader implications of the FDA’s ruling in December. The decision marked a milestone for gene therapy as a field. It was the first time the FDA had approved a genetic treatment for an inherited condition—finally realizing the vision Bennett, Maguire and their colleagues had back in the 1980s. And it paves the way for more such therapies.

“It now sets a path for others to follow going forward, where there was none before,” Bennett says. “This is looking way down the road, but maybe not as far as you think.” ◻

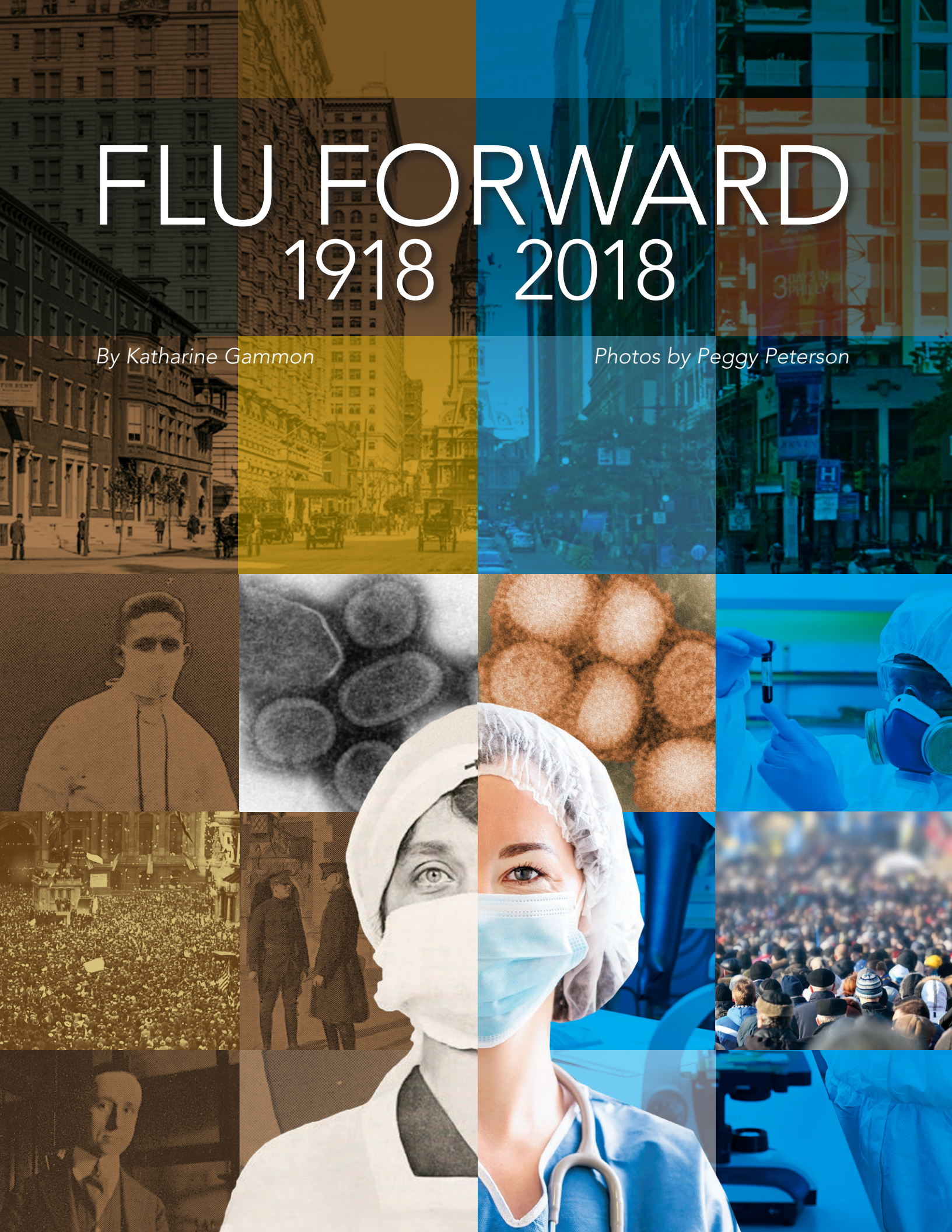
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FLU FORWARD

1918 2018

By Katharine Gammon

Photos by Peggy Peterson



Penn medical students raced to treat a flu epidemic in 1918 with few resources. Today, researchers are finding new ways to battle an old illness—because the threat of another major global pandemic is not as far in the past as we might think.

The summer of 1918 in Philadelphia was hot and sticky. Isaac Starr had just finished the second year of medical school at the University of Pennsylvania. The First World War was raging, but it still seemed far away in Europe.

Starr spent the early summer doing research at the Marine Biological Laboratory at Woods Hole, Massachusetts. Late in August he went on a hiking trip the White Mountains with his father—and during this trip, he first heard a news report about an epidemic of influenza in Spain.

When he returned to campus in September, Starr discovered a city abuzz with activity. A freighter of soldiers was pulling into port, and many of the men were sick. When the medical school started session again, the first lecture was about influenza—a departure from the usual schedule. Unfortunately, Alfred Stengel, MD, the professor who gave the lecture, had no advice for remedies—he didn't think any existed. "For me and my classmates, knowledge of the disease we were to face so soon was limited to the contents of that one lecture," Starr recalled in an essay published many decades later in the *Annals of Internal Medicine*.

A few days after that meager preparation, Starr and his classmates received grave news: An epidemic was judged to be developing in Philadelphia. With so many medical practitioners away in the armed forces, medical students' services were needed in caring for the sick. School was closed for third- and fourth-year students.

Over the next few days, medical students and city workers constructed a temporary hospital with wooden partitions, based on the skeleton of Philadelphia's Medical-Chirurgical Hospital at 18th and Cherry Streets, then recently shuttered to make way for construction of the Benjamin Franklin Parkway. The building had five floors, each containing about 25 beds. Then they waited.

Soon the patients poured in. At first, nobody on Starr's floor was very ill—the patients had fever but little else wrong with them. But over a few days, their illness changed for the worse. The patients' lungs filled with sticky phlegm, and they became short of breath. "After gasping for several hours they became delirious and incontinent, and many died struggling to clear their airways of a blood-tinged froth that sometimes gushed from their nose and mouth," Starr writes. "It was a dreadful business."

Before the flu epidemic ended, the illness swept the globe. An estimated 50 to 100 million people died worldwide—and one-third of the total human population was sickened. Philadelphia, the hardest-hit American city, got the brunt of the illness. Strangely, many of the people who were the sickest were in their twenties, even though, typically, babies and elderly have the worst flu outcomes—so the tragedy was compounded by the virtual loss of a generation, not to war, but to pandemic.

The influenza of 1918 ravaged the world and then went away, without explanation, and without reassurance that a similarly deadly global pandemic could not happen again. A century later, we know much more about the 1918 outbreak, about preventing influenza, and about surveillance that can identify the next pandemic before it takes hold. We also know that there is no use wondering *if* there will be another outbreak, but only *when*—and how much better prepared we will be to handle it when it strikes.

The Quest to Intervene

From the start, researchers fought to figure out what the illness was. On Sept. 21, 1918, just days after the first civilian flu cases were confirmed, Paul A. Lewis, MD, of the Henry Phipps Institute at the University of Pennsylvania, claimed to have determined the cause of the disease—a bacterium known as Pfeiffer's *B. influenzae*. The *Philadelphia Inquirer* wrote that Lewis's findings had now "armed the medical profession with absolute knowledge on which to base its campaign against the disease." Of course, Lewis was wrong; influenza is caused by a virus. But in the pre-antibiotic era, that knowledge would have made little difference.

At first, life in the city and region went on as normal. With a patriotic fervor to support the troops, a rally for the Fourth Liberty Loan Campaign brought together 200,000 Philadelphians in the city's streets on Sept. 28. Philadelphia raised vital funds for the war effort as a result—but this success came with a big downside. Within three days of the event, 635 new civilian cases of influenza signaled the beginning of the deadliest period of illness in Philadelphia's history.

Patients on the hospital wards were gasping for breath and dying. Starr reported for each eight-hour shift at 4 p.m.,



As a medical student in the fall of 1918, Isaac Starr (right) received just one lecture from Alfred Stengel, MD (left) about influenza before the pandemic struck Philadelphia.

and found few familiar patients—most had died overnight and been carried away.

“This happened night after night,” he recalls. He began to wonder if the people responsible for admissions were sending the sickest of the sick to his floor—the top floor. “The deaths in the hospital as a whole exceeded 25 percent per night during the peak of the epidemic,” he writes. “To make room for others the bodies were being tossed from the cellar into trucks, which when filled carted them away.”

Philadelphia's city morgue, built to hold 36 bodies, was now faced with the arrival of hundreds. Soon, the entire city was quarantined to try and stop the disease's spread.

The life of the city had almost stopped: Public assembly was forbidden, so there were no plays, movies, concerts, or church services. Schools were closed. Some stores and businesses stayed open, some did not.

By Oct. 4, there were 636 new cases and 139 deaths—just that day. With the city shut down, businessmen started to panic—after all, more cases meant more employee absences and fewer customers. The Bell Telephone Company ran a full-page notice in the newspapers, letting the public know that 27 percent of its operators were absent, and imploring them to avoid calling unless absolutely necessary.

In contrast with the quiet streets and empty buildings outside, Starr and his classmates struggled to keep up with

the human tragedy inside the makeshift hospital. Starr had started off thinking of himself as a nurse, prepared to carry out orders from a doctor. To his surprise, he was the only medical professional his patients would see. He was alone in making decisions. While sick patients writhed around him, he made sure to wear a mask, gown, and wash his hands religiously. Very few doctors got sick in the hospital.

It wasn't easy to find treatments. At the Philadelphia College of Pharmacy and Temple University, administrators decided to suspend classes so that pharmacy students could help fill prescriptions. Most were for whiskey: Since saloons were closed, alcohol was available only in drugstores. People began to try out home remedies like goose-grease poultices, sulfur fumes, onion syrup, and chloride of lime.

Inside the hospital, the supplies weren't much better. The hospital had tanks of oxygen but no effective way of administering it. Starr had two ideas for possible treatments: atropine, a nervous system blocker, and camphor oil, a stimulant. Starr was convinced that atropine was worthless, but he thought camphor helped a bit. From time to time, Starr found that a patient's pulse would pick up after an injection—but the patients soon died nonetheless.

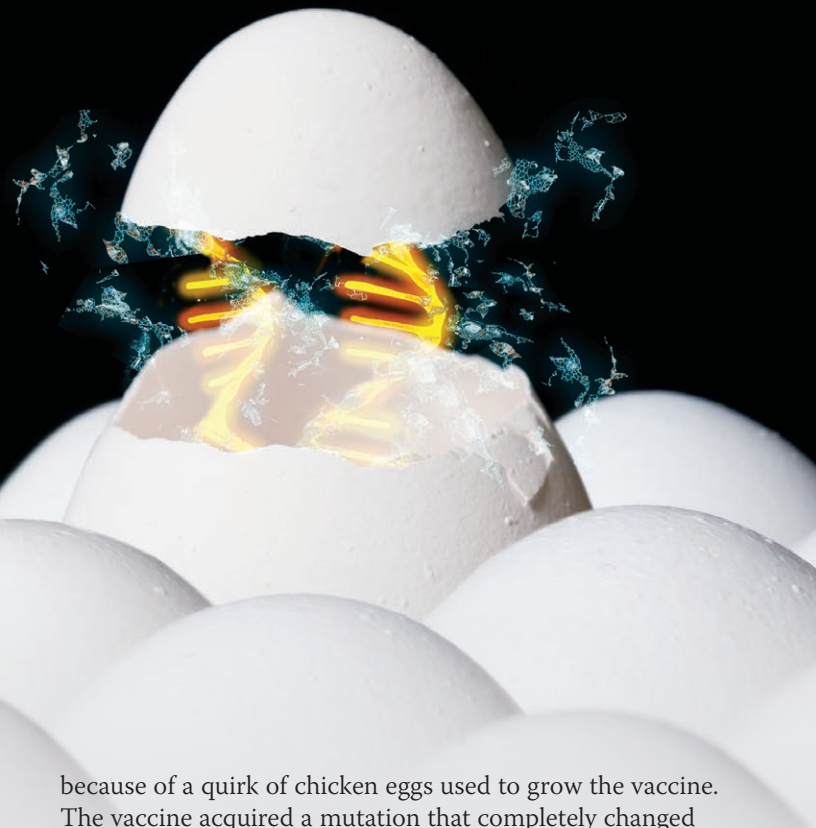
Of course, today's medical system is completely different from the overcrowded, low-resource system of 1918. Hospitals today have good antibiotics, surveillance, and better supportive care. “So even if a serious virus came about, it's likely we would see less overall mortality,” says Scott Hensley, PhD'06, an associate professor of Microbiology at the Perelman School of Medicine who studies human antibody responses to influenza and other viruses, and who has taken an interest in the 1918 pandemic. He notes that many of the

An estimated 50 to 100 million people died worldwide from the 1918 influenza pandemic—and one-third of the total human population was sickened.

deaths in 1918 were from secondary bacterial infections; if a similar outbreak happened today, the widespread use of antibiotics would limit mortality.

Ebbing Lautenbach, MD, MPH, MSCE'01, chief of the division of Infectious Diseases, Robert Austrian Professor of Medicine, and a professor of Epidemiology, adds that there are systems in place at the local, regional and federal level to identify infectious diseases early enough to deploy containment and prevention strategies. Lautenbach points to the recent example of Ebola. “The high mortality rates in West Africa were due in large part to a lack of public health infrastructure and limited resources in healthcare facilities there,” he says, adding that the high cost of supportive care meant facilities there were not equipped to care for infected patients. For Ebola cases in the U.S., the outcomes were

Future Imperfect Prevention



Modern public health planning for the flu involves a bit of future-casting: Based on the virus that is circulating in the southern hemisphere in the spring, the Centers for Disease Control and Prevention (CDC) puts together four strains in a shot for that fall's flu season in the northern hemisphere.

Sometimes, however, that prediction fails to recognize the important strains, as in 2014, when the flu vaccine was only 19 percent effective. Other times, the vaccine fails for other reasons. Hensley recently published research in the *Proceedings of the National Academy of Sciences* showing that the 2016-2017 seasonal flu vaccine had a poor rate

because of a quirk of chicken eggs used to grow the vaccine. The vaccine acquired a mutation that completely changed how the human immune system recognizes it, explains Hensley. "The vaccine itself changed its properties as it was prepared," he says.

The problem of chicken egg adaptation is not a new one—but in the 2016 vaccine, it was particularly bad. "The virus has evolved over the past years to just grow terribly in chicken eggs," explains Hensley. "The mutation that occurred last year is sort of a massive one and there's no way to get around it." His research found that vaccine grown in insect cells instead of chicken eggs didn't acquire the mutations.

very different. "In a country that has the best of modern medicine, as well as a robust public health system, our ability to screen and identify infected patients and then keep people alive while the body fights a pathogen is much greater," he says.

Still, in a large-scale pandemic today, the sheer number of sick people could again overwhelm even a strong system. In 1918, the flu sickened around a third of the global population and killed between 5 and 10 percent of those who got sick, notes Gary Kobinger, PhD, a virologist at Quebec's Centre Hospitalier de l'Université Laval, who is collaborating with a Penn team on a new vaccine strategy. "Even if less than 10 percent of the U.S. population had a severe illness and had to go to the hospital, I don't know if we would be able to support 30 million people in ICUs."

If we are lucky, the impact of most common circulating flu strains today should also be reduced by the availability of flu vaccines—but there is still that element of luck. On average, current flu vaccines are 60 percent effective against seasonal flu infections—and they require someone to get revaccinated every year, among other shortcomings (see sidebar, "Future Imperfect Prevention").

But the shortcomings of seasonal flu vaccines are minor compared to their inadequacy against an emergent pandemic strain, one that might be similar to the flu of 1918: "Current seasonal flu vaccines likely would offer no protection against a new pandemic viral strain," Hensley says. "A new vaccine would need to be created. During the 2009 H1N1 flu pandemic, a new vaccine was rushed into production but it was too late by the time that the vaccine was available to the public."

One Shot, Forever

Universal flu vaccines could circumvent the guesswork involved in making flu vaccines, as well as the need for an annual shot. A universal vaccine could fight all strains, including pandemic strains—for decades. This is a goal that Drew Weissman, MD, PhD, a professor of Infectious Diseases at the Perelman School of Medicine, has in sight.

It might sound farfetched, but Weissman has been creating modified messenger RNA molecules to produce any protein that the body might need. He figured out a way to make the RNA invisible to the immune system, so it could deliver a therapeutic protein to an animal as a form of



and monkeys to see if the vaccine protects them. Another issue to contend with in developing the approach as a potential human vaccine may be scaling up. Right now, his lab can make very small amounts—10 or 20 milligrams—of RNA. To immunize the world, it would take kilograms.

Hensley, who works with Weissman on this project, says he's excited about the possibilities of RNA-based vaccines and that he's amazed at high antibody responses the RNA-based vaccines elicit. He also points out that it takes a long time to make our current flu vaccine—but the RNA can be made quickly.

And time matters. No one knows when the next pandemic will arrive, but the experts agree: It's not a matter of if humans will be hit with another devastating virus, but when. Flu is a fluid, adaptable virus, with reservoirs in pigs and birds, so there's no telling from where the next virus will pop up. Influenza infections are the seventh leading cause of death in the U.S. and result in almost 500,000 deaths worldwide per year, according to the CDC.

The current technology to create flu vaccines—chicken eggs—takes 8 or 9 months to get a shot out to people. And that's not fast enough, says Kobinger, the Canadian virologist. "If we have a new strain emerging, within three weeks it will be all over the continent, based on what we learned from H1N1 in 2009," he says. Luckily, that outbreak was not a particularly deadly one—but it was lightning quick, spreading in weeks in North America and in three months around the world. "So how would you provide a vaccine

The Fourth Liberty Loan Parade brought 200,000 Philadelphians together on Broad Street south of City Hall just before the influenza pandemic intensified in the city. Scott Hensley stands at the site at present day.

treatment. Because therapeutic proteins (for example for cancer or anti-inflammatory treatments) are the fastest-growing medicines in the world, this RNA approach has taken off in research in numerous directions.

While doing this work, Weissman found he could take a standard flu antigen and deliver it as an RNA to activate a universal flu response. And the response is large in the body: The titers of antibodies produced in animal models are about 25 times higher than those elicited by the standard vaccine that people get from their doctors, he says. RNA vaccines are also in the works for rabies, HIV, Zika, and some bacterial or parasitic infections.

The flu work is still in early stages. Weissman and his team are working on animal trials with very old and young mice

in three weeks to have an impact on the first wave?” asks Kobinger. If a more severe virus came along that was equally swift, he says, “it would be catastrophic.”

Targeting the Nose

As quickly as the 1918 influenza outbreak began, it began to subside. After weeks of misery, Starr watched as the patients’ deaths on the top floor of the hospital started to wane. By the end of October, the number of patients decreased, public places reopened, and quarantines were lifted.

The type of flu was also milder as the weeks wore onward. “So, as mysteriously as it had come, the killer departed,” he writes. After about five weeks of working in the clabboard, temporary hospital surrounded by bodies, medical students went back to books and rotations. Slowly, life returned to normal. By the spring of 1919, it was estimated there were 12,191 flu deaths in Philadelphia alone—out of a population of 1.7 million.

But as the years and decades have unfolded since then, physicians like Starr, who earned his medical degree at Penn in 1920 and went on to join the faculty and served as dean after World War II, remained aware that another pandemic could occur and contemplated how, why, and where. Historians have looked back at the massive public gathering at the September 1918 Liberty Loan parade as one likely contributor to the spread of disease in Philadelphia. Perhaps they looked at other public gatherings in the aftermath and considered that, with every cough, sneeze, and droplet that flew through the air, another possible virus was upon them. We are never truly free from the threat of another viral pandemic.

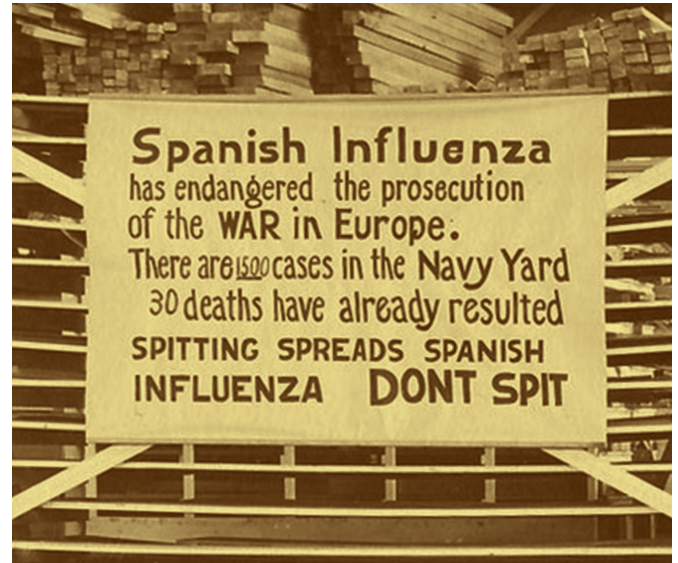
But while droplets carry viruses, they also carry information—and they might be one way to stop future pandemics.

“It seems crazy that we’re developing a systemic response to block something like the flu—an infection around the nose,” says James Wilson, MD, PhD, director of the Gene Therapy Program, Rose H. Weiss Professor and director of the Orphan Disease Center, who is working on a gene-ther-

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apy flu vaccine that elicits a faster immune response than traditional vaccines in part because it intercepts the actual path of the virus. The infection gains entry into a body through breathing in someone’s cough or sneeze. You may not get sick for many days—but the virus is slowly amplifying in the nose. Eventually the virus gets to your lungs by getting inhaled through your nose.

“Our strategy was developed to prevent the virus from gaining entry into the lungs,” explains Maria Limberis, PhD, a research associate professor and executive director of the Program in Comparative Medicine at Penn Gene Therapy Program, who initially began working with Wilson as a post-doctoral fellow in his lab. “These viruses replicate quickly to bypass the immune system, infect the lungs, and cause disease.”



Public health officials knew in 1918 that droplets of saliva and sneezes would spread disease.

This is a comparatively new entry strategy for Wilson, who had been working on gene-therapy approaches to fight HIV and other viruses for years before considering flu. The big idea is to take the gene encoding a therapeutic protein, clone it into an adeno-associated virus (AAV) vector, and inject the vector. That would program a patient’s cells to express the therapeutic protein. AAV is a huge change in the way vaccines work because it programs non-immune cells to express antibodies against a pathogen.

Then Bill Gates, who had taken a personal interest in Wilson’s work because of his long-standing desire to battle HIV, stepped in. He asked the researcher a provocative question: Could AAV be used to prevent flu? Wilson started to think about it. The problem was, muscle and liver cells, which he had targeted with gene therapies for HIV and other blood-borne viruses, wouldn’t work against the flu because it spreads through the air. Targeting airway cells seemed like a good pivot of the technology. Wilson enlisted Limberis to collaborate on the project because she was experienced with using AAV vectors in epithelial cells like those lining the nose from her work in gene therapy for cystic fibrosis. Kobinger, the Canadian virologist who also completed a postdoc in Wilson’s lab, rounded out the team.

In 2012, the team started the work with a simple experiment. They took several known flu antibody sequences, cloned them into one of the AAV vectors, injected the vectors into mice, and challenged them with a common strain of H1N1 flu.

“If this antibody was effective against every major strain in the last 100 years, it should be effective in the future.”

– James Wilson, MD, PhD

Limberis remembers telling Wilson the experiment didn't work—because the treated mice survived and the non-treated mice didn't, and that was too perfect. “I couldn't believe it would work so efficiently, especially the first time we tried it.” The team eventually reproduced the results and Limberis was convinced.

From there, the team started working on more antibodies. They wanted to find out if their results were just an academic success, or if they could have applications in the real

world. The team tested the technology against lethal doses of clinical isolates of flu including H1N1 and a strain of the 1918 flu that had been reconstituted from human tissue by a member of the team Kobinger then headed in Winnipeg.

In 2013, they published the results in *Science Translational Medicine*. The mice and ferrets who received a single dose of an AAV vector expressing a broadly neutralizing flu antibody into their nasal passages were protected from the viruses, and the untreated animals were not.

Their work began to get attention from federal defense agencies for its potential application to protecting from bioweapons, and they collaborated with several programs, trying to find the ideal, broadly active flu antibodies to take this AAV technology into clinical trials. This team has recently formed a collaboration to license this technology to Janssen Pharmaceuticals, Inc. and is rapidly moving toward

Early Exposures

In the century that has transpired since the influenza pandemic in 1918, there is one enduring mystery for which our answers are incomplete. Why were so many young adults killed by the virus? That was an abnormal age distribution for an illness that usually kills babies and the elderly.

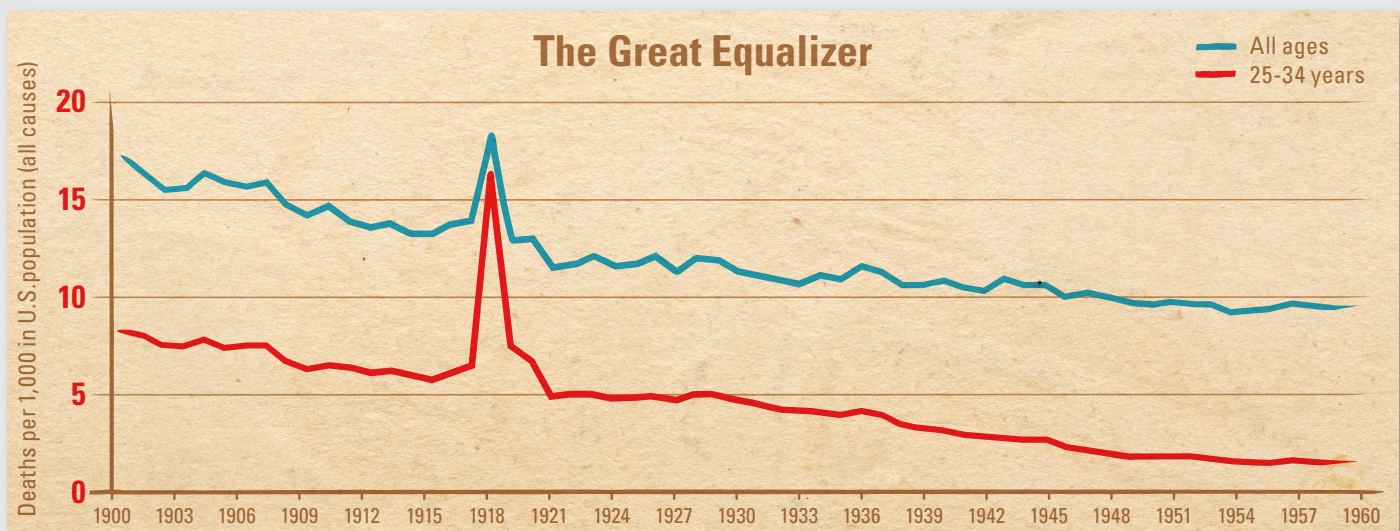
Scott Hensley has an idea of why that happened. When analyzing the pandemic H1N1 flu (another swine flu) from 2009—a particularly bad flu in terms of virulence—his lab found most people had some H1N1 immunity. But when they dissected the specific antibodies within individuals, the team found something strange: People of different ages mounted different types of immune response that recognized the virus in different places. Those responses were based on the type of flu that each person had first encountered in childhood.

“There is something magical about childhood,” Hensley says. “Many different B cells [responsible for creating anti-

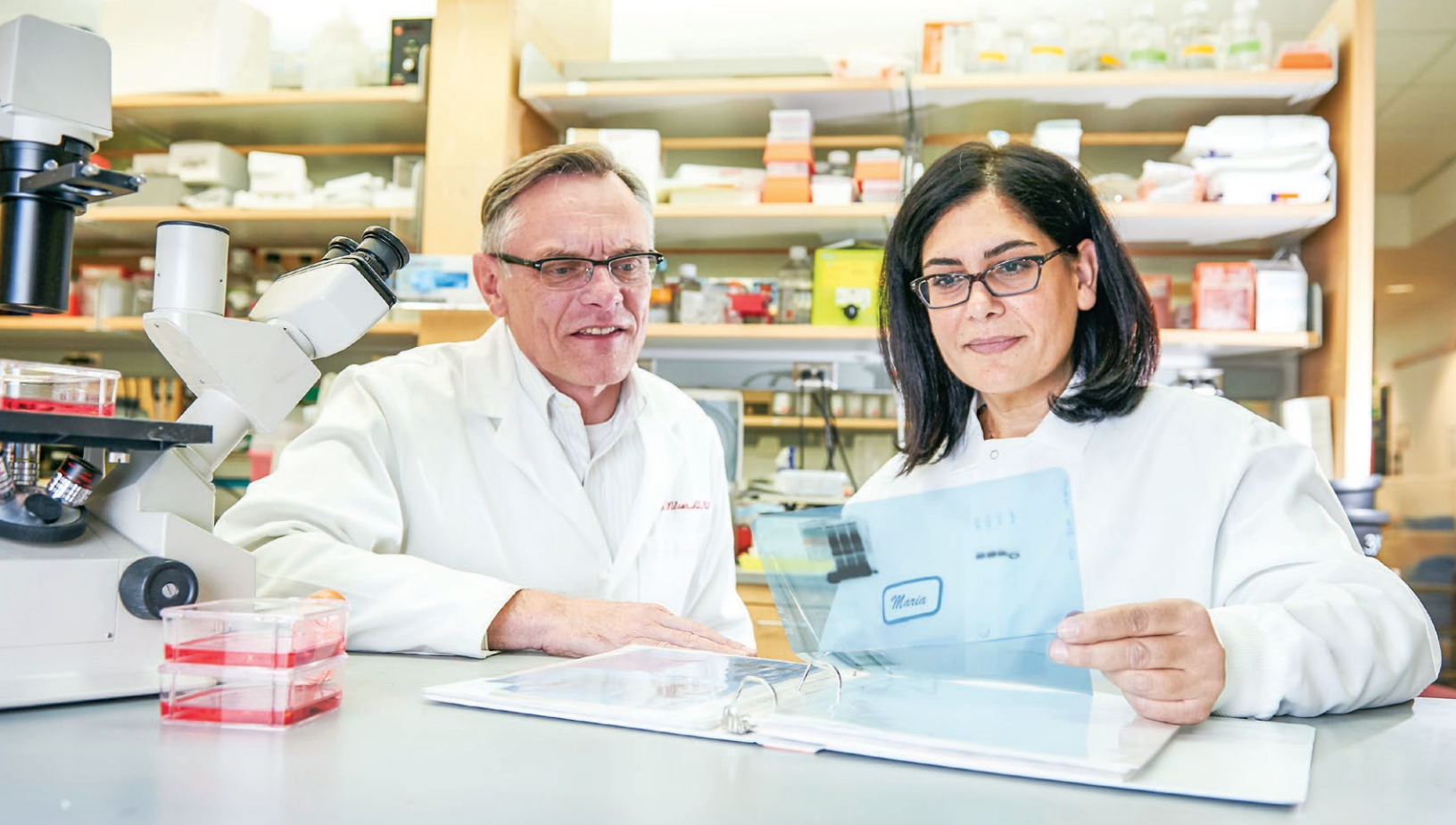
bodies] are activated during initial childhood infections and some of these differentiate into memory B cells that hang around a long time. And when we're infected later in life, these memory B cells become reactivated and dominate our responses against new viruses.” As a result, a person's antibody response narrows over time, and that can be dangerous: Single mutations in an evolving virus can prevent antibodies from binding.

This might explain the disproportionate deaths of young adults during the 1918 flu.

It's possible, says Hensley, that people born around the 1890s were exposed to a virus in childhood that made them more susceptible to the 1918 flu. He adds that children today get their first flu exposure from a vaccine and not from the live virus, so it's an open question how this first exposure will impact their antibody response in the future.



Typically, adults in their prime are far less likely than other age groups to die from influenza or any other cause. The deadly pandemic nearly obliterated that gap in 1918 because people in their 20s and 30s were disproportionately affected.



James Wilson, MD, PhD, and Maria Limberis, PhD, are testing gene therapy in the nose to block inhaled flu viruses from taking hold.

Phase 1 trials utilizing AAV vector gene therapy to deliver Janssen's proprietary anti-influenza antibody. The trial will target people over the age of 65, who have a particularly bad outcome with flu—and for whom existing vaccines are only 20 percent effective.

Like Weissman's RNA vaccine, the AAV vaccine is a hoped-for universal vaccine—one that might work against most or all flu strains without requiring the annual guesswork involved in predicting regular annual flu strains. "If this antibody was effective against every major strain in the last 100 years, it should be effective in the future," Wilson says.

Another advantage of the AAV vector vaccine is how quickly it works: Normally, it takes 2 to 3 weeks for a person's immune system to get activated—but this method expresses antibodies within 24 hours.

If safe and effective, the AAV vector vaccine could thus also subsequently be considered as part of a pandemic flu response for the healthy population. (But don't look to this work to create protection forever. When it goes into the nose and targets epithelial cells, it lasts 4 to 5 months in monkeys for safety reasons, Wilson says.)

Using AAV as a vehicle, a vaccine could get people protected against influenza within weeks rather than the months required to grow traditional vaccines in chicken eggs. Kobinger explains that once researchers identified a new strain, they could sequence it within a week. And with that genetic information, scientists could make antibodies very quickly. "In theory, you get protected within two months rather than six or eight." He could envision a future where someone could go to the pharmacy and get a dose to inject themselves within a few weeks of the start of an

outbreak. This method could help in urgent pandemics beyond flu like Ebola, SARS, MERS—any disease that's spread through the air.

Past is Prologue

"There is good reason to believe that a future epidemic could be handled much more effectively than was the last," Starr wrote in his *Annals of Internal Medicine* essay recalling his ordeal in 1918. He penned the piece in 1976, when the U.S. was facing the threat of a novel swine flu, feared at the time to be the next great pandemic. He notes that boring-but-important efforts like hand washing and gowns helped medical professionals stay healthy. And antibiotics and supportive care would keep many more people alive in future pandemics. Even more innovations that Starr could not yet imagine—RNA vaccines and AAV vector vaccines among them—still lie ahead. These could rapidly confer immunity against more flu strains and change the game—for people now and in the future.

But the big question for the future that no one can answer is when the next pandemic will happen.

"All bets are off the table because we can't forecast this," says Hensley. "We don't know how pathogenic the next strain will be. We have come a long way but have much more still to learn if we want to be better prepared for the next pandemic." □

► **After his dramatic turn as a pandemic flu doctor during medical school, Isaac Starr went on to have a distinguished career through a century that saw major changes in medicine. Read more about his story, among other related links, at PennMedicine.org/magazine/1918**

PENN PHYSICIANS GAIN NATIONAL AND DONOR RECOGNITION FOR INNOVATION

A Celebration of Philadelphia's Next Revolution: Immunotherapy

Former Pennsylvania Governor Edward Rendell and Richard Vague joined forces to pay tribute to Penn Medicine's breakthrough immunotherapy success at an event dubbed "Philadelphia's ImmunoRevolution." It was held—most fittingly—at the Museum of the American Revolution, and celebrated Penn discoveries that culminated in last summer's FDA approval of CAR T therapy for some patients with relapsed acute lymphoblastic leukemia.

"The most important thing we can bring to the human race is hope," Rendell said. "This is what Penn Medicine's ImmunoRevolution is doing: bringing hope and turning the world's eyes, once again, to Philadelphia."

Speaking to the business and philanthropic leaders gathered that evening, Dean J. Larry Jameson, MD, PhD, likened the forward-thinking partners who helped seed this research at Penn to those who led the American Revolution. Guests then heard from Penn's own immunotherapy visionaries: Abramson Cancer Center Director Robert Vonderheide, MD, DPhil; Carl June, MD, who first pioneered CAR T cell immunotherapy; Saar Gill, MD, PhD, who is investigating the next generation of CAR T cell therapy; and E. John Wherry, PhD, director of the Institute for Immunology.

▶ **To learn more about joining the revolution, be sure to watch the inspiring ImmunoRevolution video, available online at PennMedicine.org/immunorevolution, and contact Senior Executive Director for Development and Alumni Relations Tricia Bruning at 215-898-0578.**

The Honorable Ed Rendell



Carl June, MD



From L-R: Saar Gill, MD, PhD; John Wherry, PhD; and Robert Vonderheide, MD, DPhil



From L-R: Ron DeMatteo, MD; Patrick Reilly, MD; William Schwab, MD; Clyde Barker, MD; and Ralph Muller



From L-R: Patrick Reilly, MD; Michele Volpe; and William Schwab, MD



Dean Jameson with Patrick Reilly

A First for Division of Traumatology, and an Honor for Its Founding Chief

Recognized as one of the best in the world, Penn's Trauma Center recently received a well-deserved honor with the creation of its first endowed professorship. The **C. William Schwab, MD Endowed Professorship in the Division of Traumatology, Surgical Critical Care and Emergency Surgery** was established with the help of generous Penn Medicine friends, most notably lead donors Pina Templeton and the Haas Family. The chair was inspired by the friendship and shared dedication of two renowned trauma surgeons, Drs. Bill Schwab and Jack Templeton (Pina's late husband). Schwab, the division's founding chief, is known around the globe for his contributions to the field.

"Dr. Schwab poured his passion for trauma care into building Penn Medicine's outstanding trauma division," said J. Larry Jameson, MD, PhD, dean of the Perelman School of Medicine. "This professorship is wonderful recognition of his vision and guidance, and I am proud that the Schwab chair will empower other great physicians to make even more life-saving advances."

Patrick Reilly, MD, FACS, the current chief of the division and beloved leader in mentoring young physicians, was selected as the inaugural chairholder. Reilly came to Penn for his fellowship, and joined the faculty in 1995. For 18 years, he was program director for the fellowship program. Widely known for his work in trauma system design and how it affects injured patients, Reilly led the unit's relocation from HUP into stunning new space at Penn Presbyterian in 2015. The move has improved the trauma team's capacity to work efficiently and increased the number of patients cared for—more than 2,600 last year.

Penn Medicine has bestowed more than 200 endowed professorships, which are integral to sustaining scholarship, advancing patient care, and accelerating research in an academic medical center of Penn Medicine's caliber.

► **If you are interested in supporting Penn's Trauma Center, please contact Senior Executive Director for Development and Alumni Relations Kim Grube at 215-898-0578. To read more about the Trauma Center, visit http://www.uphs.upenn.edu/surgery/Clinical/Trauma/trauma_home_page.html.**

Send your progress notes and photos to: Donor Relations Penn Medicine Development and Alumni Relations 3535 Market Street, Suite 750 Philadelphia, PA 19104-3309 medalum@dev.upenn.edu

1960s

Ronald S. Banner, MD'67, published three articles in 2017. "The Best Possible Health Care" appeared in two parts in the *International Journal of Healing and Caring*; "On Being a Doctor" appeared as a special guest feature in the spring issue of the Newsletter of the Pennsylvania Society of Chaplains. He practices internal medicine in Northeast Philadelphia.

1970s

Matthew F. Gutowicz, Jr., MD, GME'77, has been appointed to the advisory board of Essential CRE Inc., the sister company of Radiology International, an organization which coordinates CRE Conferences for radiologists worldwide. He is a diagnostic radiologist in La Quinta, Calif.

Stuart A. Lipton, MD'77, PhD'77, was named professor and inaugural co-director of the Neuroscience Translational Center at the Scripps Research Institute in La Jolla, Calif. Lipton is also professor of Neurosciences and a clinical neurologist at the University of California, San Diego, School of Medicine. In his new position, Lipton is developing and testing new treatments for Alzheimer's, Parkinson's, and autism spectrum disorder.

1980s

Lewis Wetstein, MD, GME'82, has been awarded the Arthur Ellenberger Award of Excellence in State Advocacy from the American College of Surgeons. He is the president of the Medical Society of Monmouth and Ocean Counties, and a clinical

associate professor of Surgery at Robert Wood Johnson Medical School at the University of Medicine and Dentistry of New Jersey.

2000s

Jonathan J. Hogan, MD'07, GME'10, has been appointed to the medical advisory board of Dimerix to help guide the DMX-200 clinical program. He is clinical director of the Penn Glomerular Disease Center, and an assistant professor in Nephrology at the Perelman School of Medicine.

2010s

Alana M. Feiler, MD'12, GME'15, has joined Lancaster General Health Physicians practices, at its LG Health Physicians Hospitalists. She recently completed an internship and residency at the Hospital of the University of Pennsylvania and Children's Hospital of Philadelphia.

OBITUARIES

1950s

H. Newton Spencer, MD'50, GME'58, an orthopaedic surgeon; Nov. 3. After completing an internship at Presbyterian Hospital in 1951, he served as medical director at Cannon Mills in Kannapolis, N.C. In 1953, Spencer served as an Air Force flight surgeon. After his military service, he completed a residency in orthopaedic surgery at Penn in 1958. After earning a certificate from Harvard University Graduate School of Business Administration in health systems management in 1973, he developed a network of clinics that completed pre-employment exams and medical assessments for workers. He is survived by his wife Mary Johnston Spencer BA'44, MD'48.

Allen E. Yeakel, MD'51, GME'61, an anesthesiologist; Oct. 22. He served in the U.S. Navy from 1944 and was honorably discharged in 1946 and en-

listed in the USN Reserve. He completed his internship at Philadelphia General Hospital and his residency in anesthesiology at the University of Pennsylvania. He served as a professor and founding chair of the Department of Anesthesiology at the Pennsylvania State University School of Medicine at the Milton S. Eisenhower Medical Center. In 1976, Allen left academic medicine and returned to private practice working at Lancaster General Hospital until he retired in 1990.

George E. Ruff, MD'52, emeritus professor of Psychiatry; Sept. 29. He completed a psychiatric residency at the University of Michigan. From 1957 to 1959, as an Air Force investigator of stress and fatigue, he helped choose America's first men to go into space. In 1959, he joined the Psychiatry faculty at Penn. He served as associate dean of the medical school from 1975 to 1980. With Gary Gottlieb, he established the section of geriatric psychiatry, and was research director for the Research and Training Center in Aging. He retired from Penn in 1995 as professor emeritus, but continued his private psychiatry practice.

James Cox, MD'53, a retired psychiatrist; Sept. 12. Cox spent many years as chief of staff and president of the staff at the Institute of Pennsylvania Hospital and was proudest of his work with schizophrenia patients. Cox was also socially active in the University City section of Philadelphia, co-founding and leading the neighborhood's racially integrated swimming pool that opened in 1964.

Gordon K. Danielson, BA'52, MD'56, GME'63, a cardiovascular surgeon; Oct. 2. He was associate surgeon and chief of Cardiac Surgery at University Hospital in Lexington, Ky., then was recruited by the Mayo Clinic in Rochester, Minn. and worked as a cardiovascular surgeon and educator from 1967-2002. He was selected by the U.S. State Department for a joint USA/USSR congenital heart disease exchange program and traveled to the USSR several times. He contributed over 800 articles to medical journals.

1960s

Wendell B. Whitacre, MD, GME'60, GME'71, a plastic surgeon; Oct. 20. He earned his medical degree from The Ohio State University College of Medicine in 1955. He trained in general and plastic surgery at Penn. He had a plastic surgery practice in Tucson from 1962 to 2006. He was awarded the 2003 Pima County Medical Society Physician of the Year and he held academic medical positions at the University of Arizona.

1970s

Paul Gschwend III, MD'70, GME'77, a surgeon; October 22, 2017. His training at the Graduate Hospital of the University of Pennsylvania was interrupted when he was drafted during the Vietnam War to serve as a medical officer in the U.S. Navy in Indian Head, Md. He returned to Lancaster, Pa. to practice general surgery for 22 years. He served as chief of Surgery and also as medical staff president at what was then St. Joseph Hospital. He also served as president of the Lancaster City and County Medical Society, and helped to establish the Edward Hand Medical Heritage Foundation.

2010s

Danielle Peress, MD, a second-year fellow in Maternal-Fetal Medicine; Nov. 26. A graduate of Cornell University, Peress attended Mount Sinai School of Medicine and completed her residency in Obstetrics and Gynecology at Northwestern University Prentice Women's Hospital before beginning her fellowship at the Hospital of the University of Pennsylvania. Peress was a published author of research on preterm birth and other obstetrical topics, and of a first-person essay in the *New York Times* detailing her experience with cancer diagnosis and treatment while continuing to practice as a physician.

FACULTY

Carole Marcus, MBBCh, an international leader in pediatric sleep medicine; Nov. 19. A professor of Pediatrics at the Perelman School of Medicine and Children's Hospital of Philadelphia, Marcus was director of the Sleep Center at CHOP. Marcus grew up in South Africa and obtained her medical degree at the University of the Witwatersrand. She completed residency training at SUNY, Brooklyn and fellowship training at the Children's Hospital of Los Angeles. She was a member of the faculty at Johns Hopkins from 1991 to 2003 and was then recruited to CHOP and Penn. As a clinician, clinical investigator, and educator, she impacted countless patients through her unique clinical expertise and her high impact patient-oriented research. She worked closely with colleagues at Penn as associate director of the Institute for Translational Medicine and Therapeutics. Marcus held virtually every leadership position in pediatric sleep medicine during her abbreviated career and received numerous awards, including the William C. Dement Academic Achievement Award in Sleep Medicine.

Emile Mohler III, MD, a leader in vascular medicine; Oct. 13. Mohler was a professor of Medicine and founding director of the University of Pennsylvania Vascular Medicine program. Mohler graduated with honors from Boston College in 1983. He studied physiology and earned his medical degree from Georgetown University, where he also performed his residency in Internal Medicine. Mohler performed his Cardiovascular Fellowship training at Indiana University Medical Center. Mohler was recruited to



Penn in 1996. Mohler led multiple important clinical trials determining the efficacy of exercise programs, cholesterol lowering agents and novel therapies, including stem cells and genes encoding angiogenic factors, in patients with symptomatic peripheral artery disease. Mohler was an internationally recognized leader in academic vascular medicine. He authored over 250 manuscripts seven books. He was a fellow of the American Heart Association, American College of Cardiology, the American College of Physicians and Society for Vascular Medicine. Throughout his tenure at Penn, Mohler served as the "go-to" consultant for patients with complex presentations of vascular disease and was also recognized as an exceptionally gifted and committed teacher. Many of his trainees went on to lead major academic programs. Mohler's medical memoir was published in *Vascular Medicine* in October 2017.

George E. Ruff, MD. See class of 1952.

Alan Schreiber, MD, leading immune-hematologist; Oct. 2. During his more than four decades at the University of Pennsylvania School of Medicine, Schreiber served as assistant dean for research and chair of the Graduate Group in Immunology. He attended Einstein College of Medicine in the Bronx on full scholarship and completed his residency at the University of North Carolina. During subsequent training at the NIH and at the Robert Bent Brigham Hospital of Harvard University, he developed a love of immunology. He was recruited to become one of the original members of Penn's Hematology-Oncology division. He became an internationally recognized immuno-hematologist, making seminal contributions to our understanding of antibody mediated clearance of red blood cells and platelets by Fc Receptors on macrophages. Schreiber trained numerous physicians who have embarked on successful independent careers. One of his two daughters, Courtney, is an associate professor of Obstetrics and Gynecology at Penn.

LEGACY GIVING

All in the Family

A Legacy Gift Celebrates One of Anesthesiology's Most Devoted Families

Stephen Prevoznik, MD'59, GME'62, was more than a proud Penn alum: After a mentor in the department of Anesthesiology and Critical Care urged him to pursue academic medicine, he would go on to serve as a faculty member in the department—now in its 75th year—for the entirety of his career.

More than that, Anesthesiology became a second home to the entire Prevoznik family. "The department represented such a vital part of our lives," said Rita Prevoznik, Stephen's wife. "We socialized and became close friends with his colleagues, and our eight children would all get jobs in the department before three launched their careers in medicine or related fields." It was this intertwined family history and Stephen's love of teaching that helped inspire his first gift. Noticing that the department was seeing a dramatic increase in residencies, he became concerned about the availability of funding for residents, especially chief residents, that he so enjoyed training. "Although he was intimidating to department residents in particular—he was tall, with a big build and a deep voice—Stephen was able to quickly put them at ease, and he really championed their cause," Rita explained.

"Even though we didn't have much money then, Stephen established the Prevoznik Residents Anesthesia Fund in 1977," she said. Twenty years later, to help the department that he cherished, Stephen added to the fund with a charitable remainder trust.

The family connections to the department continue well past Stephen's death in 2002. Anesthesiology established the annual Prevoznik Lecture on Leadership in 2006; son Michael Prevoznik, L'88, delivered the inaugural lecture, "Effective Leadership With or Without Authority." And Rita is making her own contributions to both Prevoznik funds.

"I am heartened that Stephen and I could instill in our children a deep appreciation of the importance of philanthropy and the ability to act on it," she said, "and my family hopes, in this diamond jubilee year for the department, that the Prevoznik funds will help it remain as successful as it has been for its first 75 years." □



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► For more information, please visit our website at: www.plannedgiving.med.upenn.edu.

By Karen Kreeger

Tick, Tock, Track and Heal the Body 'Round the Clock

The timepiece a person wears on his wrist keeps one record of the day's 24-hour cycle. The tissues and cells inside that person's body keep many more. Fine-tuned by environmental cues, such as light, to the 24-hour solar cycle, the body's molecular circadian clock coordinates its rhythms. A master clock in the brain communicates that control to molecular clocks in peripheral tissues. In humans, many aspects of physiology, including body temperature, levels of blood sugar, insulin, hormones, and neurotransmitters vary on a daily cycle.

And it is becoming abundantly clear that those rhythms matter when it comes to health. Physicians tell patients to take their cholesterol-lowering statin drugs at bedtime because the related liver enzymes are more active during sleep. Studies have also identified that most heart attacks occur in the early morning as the body jolts awake. And many more disease symptoms and treatment strategies are affected by the cycle of the clock: The incidence or severity of conditions such as asthma, stroke, and depression exhibit daily variation. Similarly, the levels of molecular targets of many drugs oscillate, as do enzymes and transporters relevant to drug metabolism. Researchers are paying close attention.

An Algorithm to Find and Timestamp Hidden Cycles

Researchers from Penn Medicine and Cincinnati Children's Hospital Medical Center have developed a powerful tool for detecting and characterizing some of these molecular rhythms. They developed a machine learning-type algorithm called CYCLOPS that can sift through existing data on gene activity in human tissue samples to identify genes whose activity varies with a daily rhythm. (The acronym CYCLOPS stands for "CYCLic Ordering by Periodic Structure.")

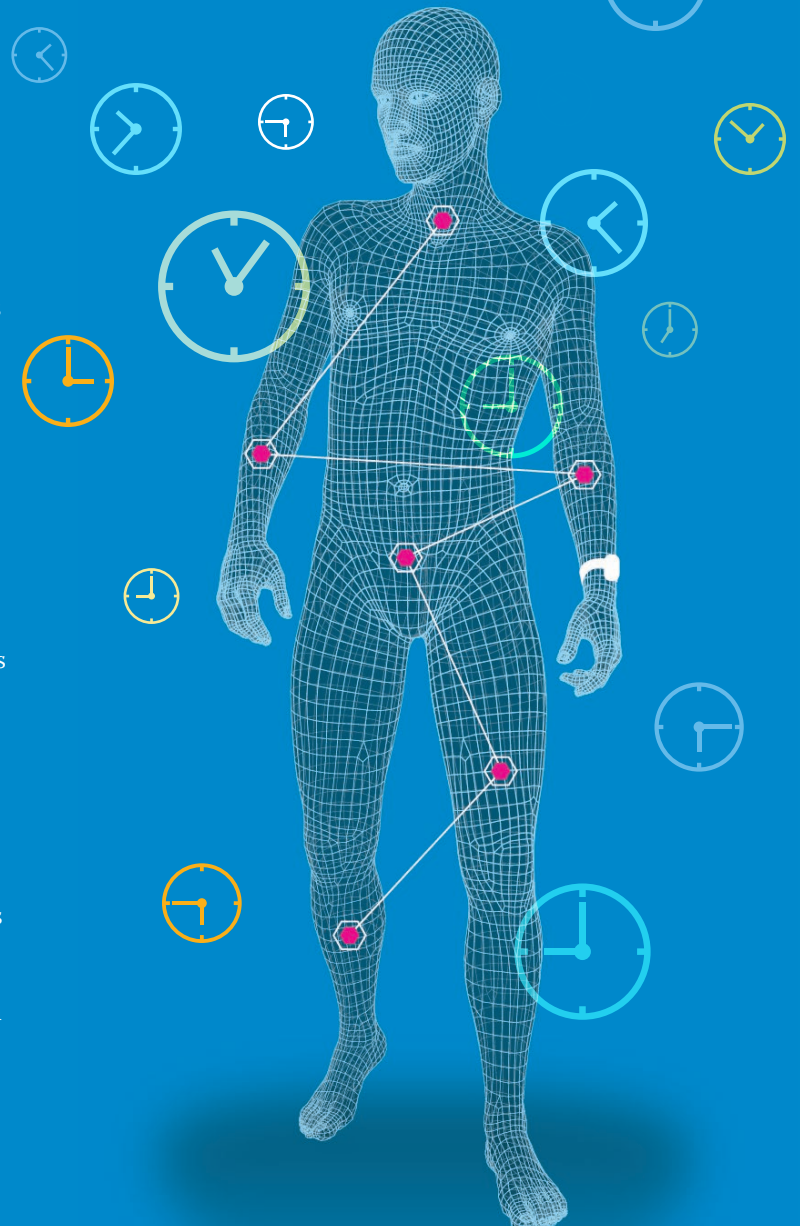
Described in the *Proceedings of the National Academy of Sciences* in April 2017, CYCLOPS at least partly overcomes what has been one of the major obstacles to studying circadian rhythms in humans.

"It's just impractical and dangerous to take tissue samples from an individual around the clock to see how gene activity in a particular cell type varies," said lead author Ron C. Anafi, MD, PhD, an assistant professor of Sleep Medicine at Penn.

CYCLOPS instead is meant to use the enormous amount of existing data on gene activity in different human tissues and cells—data obtained from people at biopsies and autopsies, in scientific as well as medical settings, and made available through databases like the federal Gene Expression Omnibus repository.

Such data almost never includes the time of day when tissue samples were taken. But CYCLOPS doesn't need to know sampling times. If the dataset is large enough, it can detect any strong 24-hour pattern in the activity level of a given gene, and can then assign a likely clock time to each measurement.

Anafi and his colleagues first demonstrated CYCLOPS to analyze gene activity levels in mouse liver cells using a dataset for which sampling times were available. Then they raised the difficulty level, asking the algorithm to generate new scientific data on human molecular rhythms. In a first-ever





analysis of human lung and liver tissue, the algorithm revealed the strongly cyclic activity in thousands of lung-cell and liver-cell genes. These included hundreds of drug targets and disease genes.

“For many of these genes, the daily variability in activity turned out to be larger than the variability due to all other environmental and genetic factors,” said study co-author John Hogenesch, a former professor of Pharmacology at Penn Medicine now at the Cincinnati Children’s Hospital Medical Center.

Underscoring the potential medical relevance of this research, CYCLOPS found strong cycling in several genes whose proteins are targeted by common drugs. In one case, CYCLOPS detected a strong circadian-type rhythm in the activity of the gene for angiotensin converting enzyme (ACE), a protein in lung vessels that is targeted by blood pressure-lowering drugs. Prior studies have found that ACE inhibitor drugs appear to work better at controlling blood pressure when given at night. “Our discovery of daily cycling in the ACE gene could explain those findings,” Anafi said.

Anafi and his colleagues are now using CYCLOPS to generate an atlas of cycling genes in different human tissues, in order to find other drugs whose dosing could be optimized by altering the time of day they are given.

Quantified Self Meets Chronobiology

When it comes to clinical studies that track 24-hour rhythms in humans, researchers often focus on a few parameters at a time and enroll many participants to see the impact of the circadian cycles across the broad population. But a recent study at the Perelman School of Medicine set this approach on its head.

The Penn team instead studied six healthy young male volunteers to collect physiological information as they went about their normal daily lives. They collected data on thousands of physiological indicators.

“We integrated data from remote sensors, wearables, and physiological samples to see how feasible it would be to de-

tect an oscillatory phenotype, the chronobiome, of an individual, despite the ‘noise’ of everyday life,” said Carsten Skarke, MD, a research assistant professor of Medicine who was first author of the study published in *Scientific Reports* in December 2017.

The study’s senior author, Garret FitzGerald, MD, director of the Institute for Translational Medicine and Therapeutics, coined the term “chronobiome” to describe the collection of an individual’s physiological traits over a 24-hour rhythmic pattern.

In their study, the majority—62 percent—of sensor readouts showed time-specific variability, including the expected variation in blood pressure, heart rate, and the hormone cortisol. Those expected results were an important baseline for the proof of concept and a necessary prelude to detect differences in the chronobiome. The team hopes to ultimately find therapeutic value in patients with circadian time-dependent diseases, such as non-dipping hypertension, nocturnal asthma, depression, and night-eating syndrome. Despite the long-recognized, time-dependent variation in the effectiveness of many commonly used drugs, there has been little use of chronotherapy in clinical practice.

The Penn team now has similar online pilot studies with surgical, HIV, heart disease, and asthma patients, as well as shift workers. The next phase of study will include 200 volunteers of both sexes and different ages, studied across seasons and when exposed to a variety of stressors.

Skarke and FitzGerald see potential for chronotherapy to become integrated into clinical care in many ways. For instance, if it’s assumed that a drug should be taken at bedtime, what does that mean for an individual chronotype? Should it be a different regimen for morning larks versus night owls? They propose that patients’ chronobiomes could be characterized using a wearable device, their cell phones, and biomarkers from their blood, urine, saliva, and feces. Then a drug could be dosed according to an individual’s chronobiome.

How soon will that become a reality in medical practice? It’s hard to say. But the clock is ticking. □



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If you are unable to complete the survey online, request a mailed paper survey by calling 215-662-2560 or by mailing a note to *Penn Medicine* Magazine, 3535 Market Street, Mezzanine/Suite 60, Philadelphia, PA, 19104.



In the Spring/Summer Issue:

African Americans, who face an elevated risk of glaucoma and worse outcomes from it, are underrepresented in research that can help find new and better treatments that could benefit them most. A vast genetic study at the Scheie Eye Institute is correcting that blind spot.

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Mindy Gray (right) knew nothing of BRCA gene mutations until after her older sister Faith Bassler (left) died of ovarian cancer at age 44. In the aftermath of that tragedy, Mindy and her husband Jon are helping to change the story for families worldwide with heritable cancer risk—and perhaps for many other cancer patients as well—through the Bassler Center for BRCA at the University of Pennsylvania.

See more on page 12.

